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THE EFFECT OF PHYSICAL TRAINING ON ANAEROBIC METABOLISM IN EMPHYSEMA

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APPROVAL SHEET

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "The Effect of Physical Training on Anaerobic Metabolism in Emphysema", submitted by Eliot Asher Phillipson in partial fulfillment of the requirements for the Degree of Master of Science (Medicine).

ABSTRACT

The purpose of this investigation was to study the effects of physical training on the mechanisms of energy production during exercise in patients with chronic obstructive pulmonary emphysema. Six male University of Alberta Hospital patients with severe, relatively pure emphysema underwent a three-week training programme consisting of treadmill walking at gradually increasing speeds. During exercise subjects breathed either compressed room air or oxygen-enriched air. Prior to initiation of training and upon completion of the programme the response to a set exercise load was ascertained utilizing a bicycle ergometer. Aerobic metabolic rates were calculated from analysis of expired air. Anaerobic metabolic rates were determined from assessment of blood lactate and pyruvate contents by calculating the rate of accumulation of total body "excess lactate".

Results of the training programme showed significant increases in walking speeds in all subjects ($P < .01$) with no corresponding increases in heart rate. The group trained on oxygen revealed a significantly faster walking speed upon completion of the training programme than the air-breathing group ($P < .05$).

Assessments of the response to exercise revealed a significant decrease in the energy expenditure for a given work load in four subjects ($P < .05$), but increases in the energy cost in two subjects, probably due to acute increases in the work of breathing at the time of the post-training assessment. Patients with emphysema were found to provide a greater than normal amount of energy requirements (13-26%) by anaerobic processes during mild to moderate

submaximal exercise. Despite changes in the absolute aerobic and anaerobic metabolic rates of exercise in all patients following training, the fraction of energy provided anaerobically was found to be completely unaltered.

It was concluded therefore that physical training of emphysema patients decreases the physiological stress, in terms of energy expenditure, imposed by exercise, but produces no changes in the ratio of aerobic to anaerobic metabolic processes utilized by such subjects in providing the energy required.

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INTRODUCTION

The management of patients suffering from chronic bronchopulmonary diseases, particularly obstructive pulmonary emphysema, has many facets. In general terms the aims of therapy are to improve ventilatory function, to prevent and treat bronchial infection, and to manage the complications associated with chronic emphysema, noteably respiratory acidosis and cor pulmonale.[12,14,73] Exercise and physical stress have often been considered deleterious to such patients with cardio-pulmonary disorders,[66] and the affected individual may in fact become an invalid "all too soon through fear or less conscious motivation, or by over-solicitous restrictions by his physician".[14]

The efficacy and necessity of a therapeutic regimen which restricts activity has been challenged at times by various medical authorities. As far back as 1553 Dr. Christobal Mendez, in the first treatise devoted to exercise written by a physician, advised that "the easiest way of all to preserve and restore health without diverse peculiarities and with greater profit than all other measures put together is to exercise well."[57] More recently, Pierce and coworkers,[66,67] and Miller et al[58] have demonstrated that physical training improves the working capacity and efficiency of emphysema patients, this improvement being noted both in terms of work accomplished and by the measurement of certain physiological variables considered to be indices of physical fitness. The latter concept, fitness, is "the ability of the organism to maintain the various internal equilibria as closely as possible to the

resting state during strenuous exertion and to restore promptly after exercise any equilibriums which have been disturbed."[21] By this definition the subjects trained in the above studies did indeed become more fit and efficient in performing physical work as indicated by decreases in heart rate, respiratory rate, minute ventilation, oxygen consumption, carbon dioxide production, and oxygen cost of exercise for any given level of activity, and by a more rapid return of these parameters to resting levels after the termination of exercise.[66] Further, the subjects demonstrated an increased capacity for work following their period of physical training.

The mechanisms by means of which physical training exerts its beneficial effects is unknown, both in emphysema patients and in normal subjects. Despite the fact that routine pulmonary function studies did not change with training in the patients of Pierce's study, a more efficient respiratory pattern was noted during exercise. Since the cost of breathing - i.e. the oxygen consumption of the respiratory muscles - is greatly increased in emphysematous patients,[13] it is conceivable that the reductions in oxygen consumption, carbon dioxide production, minute ventilation, respiratory rate, and heart rate noted above may be the result solely of the more efficient respiratory pattern and decreased cost of breathing, rather than the result of any anatomical, physiological, or biochemical changes in the "trained" muscles. If this were so, the mechanism of the effects of training could be quite simply explained.

Against such reasoning however is the fact that despite the more efficient respiratory pattern noted after training, the maximum breathing capacity of the patients increased only 1% on the average, yet their maximum oxygen intake increased 25%, indicating that the increased oxygen consumption was by tissues other than the respiratory muscles. The latter parameter, maximal oxygen intake, is a measure of the maximal rate of aerobic energy production and release, and is probably the best single physiological indicator of the capacity to perform work.[59]

Thus, it becomes clear that by some as yet unexplained mechanism physical training alters the response to stress of patients with emphysema in such a way as to increase their working efficiency and improve their degree of physical fitness.

The overall response to physical stress in any subject, emphysematous or normal, depends upon a number of inter-related factors. In general terms these include respiratory, cardio-vascular, and tissue metabolic adjustments. The former two are concerned primarily with the delivery of oxygen to exercising muscles and the removal of carbon dioxide and heat from such tissues. As a result, the factors which limit the maximal oxygen consumption in an individual are related to cardio-respiratory phenomena.[59] The third factor, the tissue metabolic response, depends upon the balance between demands placed upon exercising muscles and the ability of the cardio-respiratory response to meet those demands. The ultimate source of all energy expended in doing work is the oxidation of fuel.[5] Should the supply

of oxygen to the tissues be insufficient to meet requirements, anaerobic energy-yielding processes are called into play. There is a limit however to the degree to which activity can be maintained on anaerobic sources of energy, and thus, to a greater or lesser extent, the exercise capacity of an individual becomes dependent upon the ability of the cardio-respiratory mechanism to deliver oxygen to the cells and upon the ability of the cells to utilize the oxygen. Since patients with emphysema often have disturbances in oxygenation and circulation of blood, it seems reasonable that their ability to exercise may be diminished,[19] and that their call on anaerobic metabolic processes may occur earlier in the course of exercise and be of greater magnitude than in normal subjects. Further, it can be speculated that physical training may exert at least part of its beneficial effects in such patients by improving the delivery of oxygen to exercising muscles and hence decreasing the anaerobic component of energy production.

It was against such a background of information and reasoning that the project of this thesis was constructed. The general plan was to subject a number of patients with chronic obstructive pulmonary emphysema to a programme of physical training, before and after which their response to an exercise load would be assessed by measuring a selected number of physiological variables. The general aim of the programme was to elucidate the mechanisms by means of which energy is produced during exercise in such subjects and the effects of physical training upon these mechanisms.

Specifically, the intent was to assess aerobic and anaerobic metabolic rates during submaximal exercise and to study the changes in these rates following a period of training. It was felt that the anaerobic metabolic rate during exercise would be higher in emphysema patients than in normal subjects, but that the rate would decrease with physical training. Neither the anaerobic metabolic rate in emphysema nor its changes with training have been documented in the medical literature.

STATEMENT OF THE PROBLEM

1. THE PRINCIPAL PROBLEM

The plan of this study was to measure during submaximal exercise the anaerobic and aerobic metabolic rates of patients with chronic obstructive pulmonary emphysema before and after a period of physical training. The purpose of the investigation was to ascertain whether rehabilitative therapy does actually alter the ratio of anaerobic to aerobic metabolic processes which these patients utilize in performing work.

2. THE SUBSIDIARY PROBLEM

A secondary problem was to determine the effects on the above parameters of breathing oxygen-enriched air during the training period.

BACKGROUND INFORMATION AND REVIEW OF THE LITERATURE

1. ENERGY COST OF EXERCISE

Since the ultimate source of energy involved in all metabolic processes is the oxidation of fuel, the total cost of any exercise can theoretically be determined by measuring the amount of oxygen consumed in the performance of a given exercise. However, when an individual begins to exercise, his oxygen consumption does not rise instantly to the level that is required to supply by oxidation all of the energy that is being expended. Similarly, on cessation of exercise oxygen consumption does not immediately fall to preexercise resting levels, but rather declines as a logarithmic function of time.[5,35,77] The excess oxygen consumed during recovery above resting requirements was termed the "oxygen debt" by Hill, Long, and Lupton.[37] They suggested that the total amount of energy which could be made available during exercise even by a maximal intake of oxygen would not be sufficient to allow man to perform severe exercise were he limited to energy provided through the contemporary supply of oxygen.[38] Consequently they reasoned, the oxygen consumed during the recovery phase represented that portion of energy which had been provided during exercise by mechanisms other than oxidation - i.e. by anaerobic processes. Therefore the total energy cost of exercise included not only the oxygen consumed during the exercise period, but also the oxygen debt.

Since 1924 the concepts of oxygen debt and anaerobic metabolism have held the attention of exercise physiologists and have been the subject

of numerous investigations. However, because oxygen debt becomes apparent and hence measureable only after exercise has stopped, it has been impossible to assess anaerobic metabolic rates prevailing during exercise on the basis of measurements of oxygen consumption made following exercise. Indeed, the older concept of oxygen debt is a static one largely because of the manner of its measurement, and the notion of an anaerobic metabolic "rate" has been beyond assessment.

Accordingly, physiologists have turned to methods which enable them to measure the instantaneous rate of oxygen debt formation - i.e. the anaerobic metabolic rate during exercise. Such methods are based to a considerable extent on the measurement of lactic acid.

2. LACTIC ACID AND ANAEROBIC METABOLISM

In 1907 Hopkins was among the first to demonstrate the relationship of lactic acid to muscular contraction.[16] Specifically, he demonstrated: that muscle can contract anaerobically; that lactic acid is produced during anaerobic contraction and accumulates until the muscle is fatigued; that lactic acid disappears when the muscle is exposed to oxygen; and that less lactic acid accumulates in a muscle that is stimulated in the presence of oxygen. Shortly thereafter Myerhof[16] showed that glycogen was the source of the lactic acid and that a correlation existed between the amount of work done by a contracting muscle and the lactic acid formed. Based on these findings, Hill, Long, and Lupton formulated their classical hypothesis

which maintained that the oxygen consumed in repaying the oxygen debt was utilized primarily to convert lactic acid to glycogen following a period of exercise in which lactate had been produced as the end product of anaerobic glycolysis.[37] A small portion of the lactic acid was said to be oxidized to carbon dioxide and water during the recovery process.

The lactate concept of oxygen debt gained considerable support particularly after Hill and Lupton[36] and Long[51] demonstrated a close correlation, although not a one to one relationship, between oxygen debt as estimated from lactic acid production and oxygen debt as actually measured. Despite general agreement with this hypothesis, evidence soon appeared which questioned the validity of a constant anaerobic metabolic rate during exercise, and of assessing oxygen debt and anaerobic metabolism solely by lactic acid formation. Margaria, Edward, and Dill[53] demonstrated an absence of hyperlactatemia during exercise of less than two-thirds the maximum metabolic rate despite the formation of a measureable oxygen debt. They suggested that the lactic acid mechanism of anaerobiosis was important only in very strenuous exercise, and that an "alactic" mechanism of oxygen debt formation prevailed during mild and moderate exercise. Their work however is open to one major criticism--viz. that lactic acid estimations were done on venous blood drawn from the arm during or after running exercises. It has subsequently been demonstrated that regional venous blood samples do not reflect total body lactate with any degree of accuracy,[22,46] and hence conclusions based on such data are

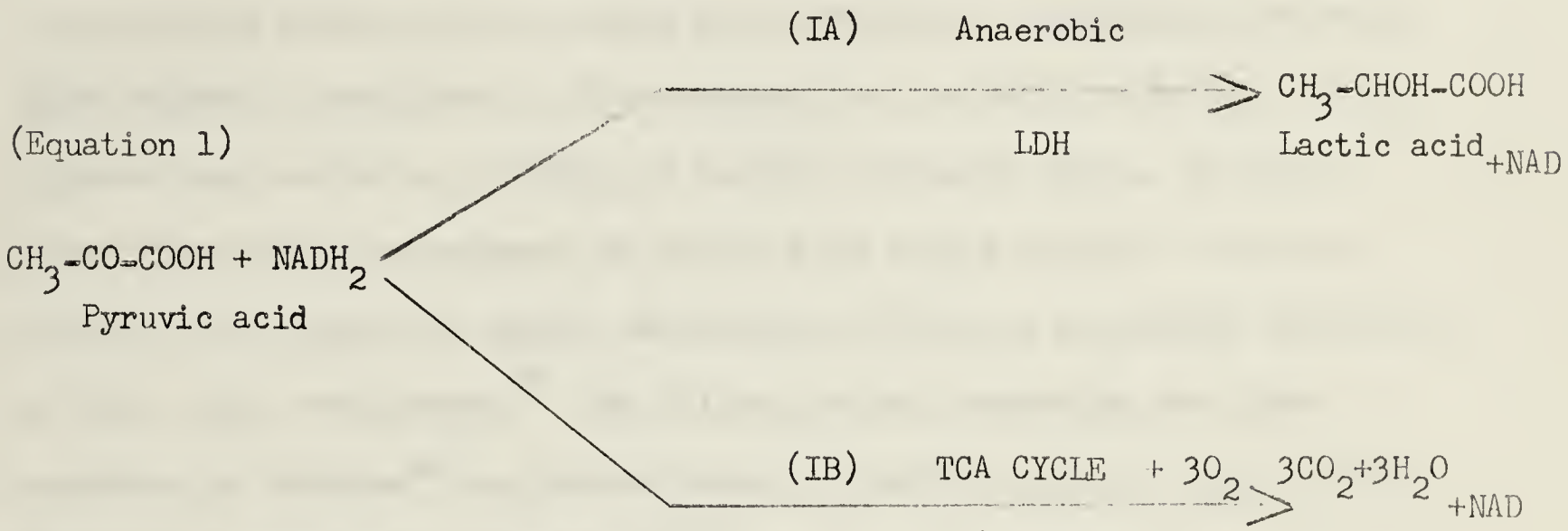
suspect. However, the concept of a constant anaerobic metabolic rate during exercise has also been challenged by Bang[4] who demonstrated an initial rise in blood lactate during exercise, followed by a gradual fall once a "steady-state" of oxygen consumption had been achieved. He postulated therefore that lactic acid is produced by anaerobic muscular activity which obtains only during the initial stages of submaximal exercise, and rejected the assumption of continuous lactic acid production.

The prevailing theory however of oxygen debt formation has been that of Margaria and coworkers[53,55,56] which postulates the presence of "alactic" and "lactic" components of the anaerobic mechanism, the former predominating in terms of time of onset, the latter in terms of quantity. This theory has generally received widespread support, and has been seriously challenged only recently by Huckabee who has developed a newer theory of lactacid anaerobic metabolism based on the concept of "excess lactate".[42]

3. THE PYRUVATE-LACTATE SYSTEM

It is convenient to separate the intermediary metabolism of carbohydrates into an anaerobic phase, referred to as glycolysis, and certain aerobic processes which include the tricarboxylic acid cycle, electron transport system, and oxidative phosphorylation.[16] The end product of the former process, glycolysis, is lactic acid, whereas the end products of complete aerobic oxidation are carbon dioxide and water. The key compound produced in glycolysis which can be either reduced to lactic acid

anaerobically or oxidized to carbon dioxide and water aerobically is pyruvic acid. Thus, depending upon the balance of factors which influence rates of anaerobic glycolysis and respiration, the disposition of pyruvic acid may take one of two pathways:



Under conditions of oxygen deficiency within cells, the oxidation of the reduced pyridine nucleotide ($NADH_2$) by molecular oxygen through the electron transport chain decreases (equation IB), thus favoring the oxidation of $NADH_2$ by the lactic dehydrogenase (LDH) system (equation IA). Accordingly, pyruvic acid is reduced to lactic acid as oxidized NAD is regenerated. Since NAD serves as the immediate oxidizing agent in anaerobic glycolysis, the latter process becomes self-maintaining in the absence of oxygen. The end product of glycolysis, lactic acid is unique in being a "dead end",[42,76] the disposition of lactate occurring only through the same LDH system that

led to its formation -- hence the interest in lactic acid as a quantitative measure of anaerobic metabolism.

The lactic dehydrogenase system may be expressed as:

(Equation 2) Pyruvic Acid + $NADH_2$ $\xleftrightarrow{LDH}$ Lactic acid + NAD

The essential feature of the system which drives the reaction to the right under anaerobic conditions is the tendency for the ratio of $NADH_2$ / NAD to increase when oxidation of $NADH_2$ by aerobic processes fails. At first glance, therefore, measurement of lactic acid should provide a reliable measure of the degree of oxygen deficiency or debt, as originally postulated by Hill, Long, and Lupton.[37] The fallacy of such reasoning was first suspected by Huckabee[42] who demonstrated the unreliability of lactic acid per se as a measure of oxygen debt.[43]

The essential feature of Huckabee's argument may be more readily appreciated by writing equation 2 in its mass action form:

(Equation 3) $$(\text{Lactic Acid}) = (\text{Pyruvic Acid}) \times K \frac{(NADH_2)}{(NAD)}$$

In this form the concentration of lactate can be seen to be dependent upon two separate factors:

1) (Pyruvic Acid)

2) $K \frac{(NADH_2)}{(NAD)}$

The second factor only is dependent upon the adequacy of oxygen supply, an increase in the $NADH_2$ /NAD ratio occurring under anaerobic states and leading to lactate production. Increase in lactate may also occur, however,

simply as a result of increases in pyruvate and apart from any changes in the $NADH_2$ /NAD ratio. The demonstration of increases in lactate related solely to increases in pyruvate under a number of conditions[42] led Huckabee to conclude that "such nonhypoxic lactate production precludes the use of lactate alone as a quantitative estimate of the anaerobic metabolism brought on by hypoxia."[42] From the standpoint of exercise studies the most important non hypoxic lactate increase produced by Huckabee was that associated with the increased pyruvate of hyperventilation."[42] (The significance of this phenomenon lies in the fact that the pK' of lactic acid is 3.86. Hence the acid is almost completely ionized at physiological pH and provides a rapid compensatory mechanism for the alkalosis which develops in hyperventilation."[42,76,79]) The mediation of these increases in pyruvate and lactate is not entirely clear, but appears to be related to the increase in pH. The importance of the phenomenon however is immediately clear -- viz. changes in lactic acid must be related to changes in pyruvic acid before the lactic acid of anaerobic metabolism can be accurately calculated.

4. EXCESS LACTATE

It is from these considerations that the concept of "excess lactate" evolved."[42] Excess lactate is that portion of lactate which cannot be related to corresponding changes in pyruvate, and hence is considered to be the result of anaerobic glycolysis. The calculation of excess lactate is

based upon the fact that the ratio of non-hypoxic lactate to pyruvate is maintained relatively constant.[42,43] Hence, that amount of lactate which cannot be attributed to pyruvate, based on their normal ratio, is termed "excess lactate" and is a measure of the degree of anaerobic metabolism resulting from tissue hypoxia.

An equation derived by Huckabee[42] is useful in calculating the amount of excess lactate (XL):

(Equation 4) $$XL = (Ln-Lo) - (Pn-Po)\frac{Lo}{Po}$$

The amount of excess lactate present at any time, n, is equal to the increase in total lactate above normal resting levels, (Ln-Lo), minus that amount which is the result of a concomitant rise in pyruvate above resting levels, $(Pn-Po)\frac{Lo}{Po}$, the normal ratio of lactate to pyruvate, $\frac{Lo}{Po}$, being taken into account.

5. EXCESS LACTATE AS AN INDEX OF ANAEROBIC METABOLISM

While both the concept of excess lactate and its application have been subject to questioning,[32,50,55,65,75,78] it is generally agreed that excess lactate probably provides a more reliable measure of anaerobic metabolism than does total lactate, although its quantitative reliability as a measure of oxygen debt is uncertain.[50,55,75,78]

The most convincing evidence in support of the concept of excess lactate has been provided by Huckabee himself who found:

1. increases in blood total lactate due to causes unrelated to hypoxia -- hyperventilation, infusions of pyruvate, and infusions of bicarbonate.[42]
2. an extremely close quantitative correlation between the oxygen equivalent of excess lactate as measured during the course of exercise, and the actual oxygen debt measured following exercise.[43]
3. a very poor correlation between total lactate and oxygen debt.[43]
4. a steady increase in total body excess lactate during exercise, indicating a constant anaerobic metabolic rate.[43-45]
5. a correlation between total body excess lactate during exercise and the ability of the cardiorespiratory apparatus to respond to the demands of exercise, both in normal subjects and in patients with symptomatic and asymptomatic heart disease.[44,45]

It is the latter two points which are of importance in regards to the project of this thesis -- i.e. that a steady anaerobic metabolic rate prevails during exercise, and that this rate is related to the ability, or lack of it, of the cardio-respiratory apparatus to supply tissue oxygen needs.

6. CLINICAL STUDIES OF ANAEROBIC METABOLIC RATE

A number of investigations have been carried out on normal subjects and athletes in whom the anaerobic metabolic rate has been measured during the course of exercise utilizing the concept of excess lactate.[11,15,44,74,75,78,50]

Although the percentage of energy which was supplied by anaerobic processes during exercise varied in different studies from less than 5%[44] to 28%,[11] comparisons between studies are difficult to make in view of the nature of the exercises, which varied from mild, steady-state, submaximal exercise to severe, maximal-output exercise, and the varied nature of the blood sampling techniques -- arterial, venous, and capillary. However, it appears that normal subjects do not supply more than 5% of their energy requirements by anaerobic processes during mild to moderate steady-state exercise.[44]

The only studies of this nature in pathological states have been concerned with cardiac patients[44,45,75,32] in whom higher than normal rates of anaerobic metabolism have been found, accounting for up to 50% of energy requirements even during mild exercise. This has been interpreted as the result of tissue hypoxia attributable to an insufficiency in the cardiac response to stress, an inadequacy which is neither indicated nor measured by cardiac output or oxygen consumption, particularly in states of compensated congestive heart failure.[44]

As mentioned in the introduction, the anaerobic metabolic rate in emphysema patients has not as yet been reported in the medical literature. However, a consideration of the response to and limitations of exercise in such patients is of interest in this regard.

7. EXERCISE LIMITATIONS IN EMPHYSEMA

A complex interrelationship of physiological abnormalities exists in patients suffering from chronic obstructive pulmonary emphysema.[7,13] The stress imposed by exercise magnifies many of these defects to the point that they become limiting factors in the amount of exercise of which such patients are capable. Unlike normal subjects in whom exercise limitations are imposed primarily by cardio-vascular factors,[59] patients with emphysema have a reduced exercise tolerance primarily as a result of dyspnea of essentially pulmonary origin.[19] Such dyspnea is apparently attributable to two factors: a reduced maximum breathing capacity; and arterial desaturation.[59] The reduced ventilatory ability and the increased work of breathing[13] which becomes even more manifest during exercise due to increased airflow resistance,[63] combine to produce dyspnea early in the course of exercise. Added to this is the effect of arterial desaturation which further stimulates respiration, leading to the sensation of breathlessness. Such hypoxemia, even in the absence of secondary heart disease, becomes exaggerated during exercise due to a further reduction in diffusion capacity[9,19] and to worsening of the already abnormal ventilation-perfusion distributions, perhaps consequent upon the higher respiratory frequency.[7]

The development of cor pulmonale usually implies the existence of additional pathophysiological phenomena which contribute to the restricted exercise tolerance. Noteable among these are: an increase in pulmonary

vascular resistance and pressure, particularly during exercise,[48,70,81] resulting probably from hypoxia,[29,31] acidosis,[10,28] and restriction of the pulmonary vascular bed;[9,70] and cardiac decompensation, often present only during exercise.[48,80,81]

The combined effects of these pulmonary, cardiac, and hematological deficits in emphysema patients results in the delivery of desaturated blood to the exercising muscles, often at rates insufficient to supply oxygen demands. It is suspected that increased anaerobic tissue metabolism results from these changes, but documentation of such is lacking.

8. THE EFFECT OF TRAINING

Physiologists have long been intrigued by the effects of physical training on the bodily response to exercise. Accordingly, the medical literature is replete with reports of studies carried out on trained and untrained subjects. The notion of physically training patients with cardiopulmonary disease is a recent one. As a result reports on the effects of such training are scanty. Extrapolation of results obtained on normal subjects, often athletes, to patients with chronic disabling diseases is contraindicated in view of the pathophysiological responses to stress which occur in the latter. Despite these differences, the few studies which have been carried out in emphysema patients indicate beneficial changes due to training[58,66,67] similar qualitatively to those which occur in healthy subjects[5,25,41,49] -- i.e. decreases in the physiological stress of exercise,

as monitored by respiratory rate, pulse rate, and oxygen consumption; more rapid return of these parameters to resting levels on cessation of exercise; and increased work capacity. Assessments of the effects of training on anaerobic metabolism in emphysema have not been made, but in normal subjects indicate improved utilization of oxygen by the muscles during submaximal exercise, and increased anaerobic capacity and tolerance to lactic acid during severe exercise.[38,40,49,71] These conclusions unfortunately were based on assessment of lactic acid per se, rather than excess lactate, and may in fact be the result simply of decreased ventilation and nonhypoxic lactatemia. However, studies based on excess lactate determinations[15] reveal an even more striking difference between trained and untrained subjects, the latter utilizing anaerobic metabolic pathways to a much greater extent despite cardiac outputs equal to those of trained subjects. This suggests that the effect of training in normal subjects is, at least in part, related either to a redistribution of capillary muscle blood flow or to metabolic adaptations in the biochemical processes of the tissues. Increased density of capillaries has been noted in trained muscles,[15,40] but direct biochemical assays of such muscles has been reported only in animal studies. It is of interest that increased muscle aldolase activity has been noted in these investigations,[34] but no changes in levels of lactic dehydrogenase,[68] malic dehydrogenase,[68] phosphorylase,[68] adenosine triphosphatase,[69] creatine phosphokinase,[69] or succinic dehydrogenase.[33]

9. THE EFFECT OF INCREASED OXYGEN

Cotes and coworkers[18,20] and Kitchin et al[48] have demonstrated that the breathing of increased concentrations of oxygen during exercise usefully increases the exercise ability of patients with chronic lung disease. This they attribute to decreased ventilatory requirements, and hence work of breathing, consequent upon relief of hypoxia. Cardiac outputs were also noted to be reduced under the influence of oxygen, attributable apparently to decreased tissue hypoxia and excess lactatemia. Likewise, mean pulmonary-arterial pressures decreased with oxygen therapy, possibly due to removal of hypoxic vasoconstrictive stimulation.

Practical application of these findings was made by Miller et al[58,67] to a group of exercising patients with obstructive emphysema. As a result of the beneficial effects of oxygen noted above, these patients were able to undertake a programme of physical training, resulting in the improvements outlined in section 8. Insofar as oxygen therapy may enable an otherwise incapacitated individual to exercise, and hence train, it is of benefit. But whether or not the oxygen per se results in long-term physiological or biochemical changes which persist beyond the oxygen-breathing period is unknown. Consequently, the ultimate effect on anaerobic processes of training with oxygen as opposed to air is unknown.

METHODS AND PROCEDURES

1. SELECTION OF PATIENTS

Because of the heterogenous nature of the underlying disorders which lead to a diagnosis of "chronic lung disease", strict criteria of selection were established in an attempt to limit the study to patients with pure chronic obstructive emphysema. These criteria included clinical, radiological, and laboratory features.

(1) CLINICAL FEATURES The study was limited to male, University of Alberta Hospital patients with obstructive emphysema of a degree that produced dyspnea within two to three minutes of walking at average speeds. Patients who were still employed in occupations requiring any degree of physical exertion were rejected. Those with histories or evidence of left ventricular disease, particularly coronory artery insufficiency, were excluded. Similarly, patients suffering from any serious illnesses other than emphysema were rejected. Also excluded were those whose past medical histories included tuberculosis, significant bronchiectasis, extrinsic asthma, or bronchopulmonary disease other than chronic bronchitis. Patients with compensated chronic cor pulmonale were accepted, including those requiring digitalis and diuretics. Of importance also in selection was a cooperative, enthusiastic attitude on the part of the candidates, and a genuine desire to improve their exercise tolerance.

All subjects were treated vigorously prior to training, with particular emphasis on tracheobronchial toilet, eradication of infection, and control of congestive heart failure. The appropriate medical regimes were maintained throughout the training period.

(2) RADIOLOGICAL FEATURES Of importance radiologically in the selection of patients was not so much positive evidence of emphysema or even hyperinflation, but rather lack of evidence suggestive of other chronic lung diseases, particularly pulmonary fibrosis and bronchiectasis. Those with signs of acute respiratory illness were similarly rejected.

(3) LABORATORY FEATURES The two most important laboratory assessments in patient selection were analysis of arterial blood and studies of pulmonary function. Those without arterial desaturation of 90% or less were rejected. Generally candidates were required to show a combination of pulmonary function defects including marked reductions in forced expiratory volumes, low diffusion capacity, poor mixing efficiency, and hyperinflation. Patients with significant restrictive defects, with or without obstruction, were rejected.

It is of interest that despite the frequently applied diagnostic label of "chronic bronchitis and emphysema," the number of patients satisfying the above criteria was very limited. However, it was considered important that a homogenous group of patients be studied in an attempt to evaluate the effects of training.

2. THE TRAINING PROGRAMME

The programme of physical training was carried out in the Rehabilitation Department of the University Hospital. Training consisted of four to five daily sessions of walking on a motor-driven, level treadmill, each walk being of ten minutes duration. The initial speed of the treadmill was determined on the basis of the pre-training exercise assessment and generally approached the subject's level of tolerance. The speed was increased every two to three days, compatible with evidence of physiological improvement. Twice daily a set number of breathing exercises was administered prior to walking.

In accordance with the subsidiary problem of the project, patients breathed either compressed air or 40% oxygen by mask during the time of walking, the composition of gas in the nearby cylinders being unknown to the subjects, other than the fact that they contained "oxygen".

The training programme in all cases was of at least three weeks duration with one day of rest weekly. During the time of day in which patients were not in training they were given portable cylinders containing gas of the same composition as that breathed when walking. This portable "oxygen supply" was used when walking about the hospital ward.

3. ASSESSMENT OF RESPONSE TO EXERCISE

Patient response to exercise was assessed prior to initiation of and upon completion of the training programme. For this purpose a Monark

(GCI Stockholm) bicycle ergometer was utilized, rather than the treadmill, in an attempt to separate the effects of practice and machine familiarity from those of actual physiological training. A work load within the patient's estimated exercise capacity was set at the time of the pre-training assessment and as closely as possible duplicated at the post-training assessment.

Subjects were brought to the research laboratory one to two hours following breakfast or lunch. It has been demonstrated[24,52] that no differences in energy expenditure occur during exercise as a result of the specific dynamic action of food. Hence fasting was not required of the subjects prior to assessment.

Following insertion of a Cournand needle into the brachial artery, patients were allowed to rest comfortably on a stretcher for at least thirty minutes. They were then transferred to the bicycle ergometer and exercised for five minutes at a constant load and rate.

All subjects, whether trained on air or oxygen, breathed room air through a Rudolph two-way valve and mouthpiece. Expired air was collected in Douglas bags for four minutes prior to bicycling and minute by minute during exercise and recovery. This gas was later analyzed for oxygen and carbon dioxide content in the estimation of oxygen consumption.

Duplicate samples of arterial blood for lactate and pyruvate determinations were drawn at rest, at one, three, and five minutes of

exercise, and at one, three, five, and ten minutes of recovery. The blood was immediately transferred into test tubes containing chilled trichloroacetic acid, the entire procedure requiring less than twenty seconds.

4. TECHNIQUES OF ANALYSIS

(1) EXPIRED AIR was analyzed for oxygen content in a Beckman model E-2 analyzer, and for carbon dioxide by means of a Godart capnograph. Volumes were measured using a gasometer (American Meter Co.).

(2) BLOOD LACTATE AND PYRUVATE CONTENT was analyzed in the Biochemistry Department of the University Hospital. The method employed for lactate determination was that of Ellis, Cain, and Williams.[27] In this technique lactic acid is converted enzymatically to pyruvic acid using the enzyme LDH and coenzyme NAD. The concentration of reduced coenzyme, $NADH_2$, formed by the process is then read spectrophotometrically, from which value the amount of lactic acid originally present can be calculated.

Pyruvate content of blood was analyzed chemically according to the method of Friedman and Haugen[30] as modified by O'brien.[64] In this procedure dinitrophenylhydrazine is employed in a reaction with pyruvic acid, forming the 2:4 dinitrophenylhydrazone of pyruvic acid. The latter, following extraction with toluene, reacts with strong alkali to form a reddish compound which can be estimated colorimetrically.

All blood samples were analyzed in duplicate for lactate and pyruvate content, the final value representing the mean of the two determinations.

(3) BLOOD WATER CONTENT required in the calculation of total body excess lactate, was measured by the method of drying to constant weight at a temperature of 93 - 97°.[26]

(4) BODY WATER CONTENT, also used in total body excess lactate estimation, was calculated according to the formula of Moore,[60,61] taking body weight and age into account. It has been demonstrated that subjects with well compensated cor pulmonale have normal body water contents[62]-- hence the above formula may justifiably be employed in this regard.

5. CALCULATIONS

(1) AEROBIC METABOLIC RATE (AMR), the oxygen consumption per minute ($\dot{V}O_2$), is equal to the difference between the quantity of oxygen inspired and the quantity expired, and was calculated from analysis of expired air according to the following equations:

(Equation 1) $$\dot{V}_{E_{ATPD}} = \text{Volume of bag} \div \text{time in mins.}$$

(Equation 2) $$\dot{V}_{E_{STPD}} = \dot{V}_{E_{ATPD}} \times \frac{B.P.}{273 + t} \times \frac{273}{760} \quad \text{L/min.}$$

(Equation 3) $$\dot{V}_{I_{STPD}} = \dot{V}_{E_{STPD}} \times \frac{FE_{N2}}{FI_{N2}} \quad \text{L/min.}$$

where $FE_{N2} = (1.0000 - FE_{O_2} - FE_{CO_2})$

$FI_{N2} = 0.7903$

(Equation 4) $$\dot{V}_{O_2} = \dot{V}_{I_{STPD}} \times FI_{O_2} - \dot{V}_{E_{STPD}} \times FE_{O_2} \quad L/min.$$

where $FI_{O_2} = 0.2094$

(2) ANAEROBIC METABOLIC RATE (ANMR) is the rate of total body excess lactate accumulation expressed as equivalents of oxygen. Total body excess lactate was calculated from the concentration of excess lactate per litre of blood water by multiplying by the volume of body water. This conversion assumes that the volume of dilution of lactate and pyruvate is approximately equal to total body water, an assumption which is apparently justified.[43,54] Total body excess lactate in milliequivalents was then converted to the equivalent number of millilitres of oxygen by multiplying by the oxygen-equivalence factor of lactate, 11.2 ml. O_2 per mEq. lactic acid. This permits the anaerobic metabolic rate to be expressed in the same units as the aerobic metabolic rate.

The formulae utilized for calculation of the ANMR were:

(Equation 5) Whole blood excess lactate (XL_B) in mEq/l:

$$XL_B = (Ln - Lo) - (Pn - Po)\frac{Lo}{Po}$$

where Ln and Pn are the concentrations in whole blood of lactate and pyruvate at any time, n, and Lo and Po are the corresponding resting values.

(Equation 6) Total body excess lactate (XL_T) in mls. O_2:

$$XL_T = \frac{XL_B \times \text{Body water content (Wb)} \times 11.2}{\text{Blood water content (BW)}}$$

$$\text{i.e. } XL_T = XL_B \times \frac{11.2\ Wb}{BW}$$

(Equation 7) $$ANMR = \frac{dXL_T}{dt} \quad \text{ml./min.}$$

(3) TOTAL METABOLIC RATE (TMR) is equal to the sum of the aerobic and anaerobic metabolic rates, both expressed as mls. O_2 per minute.

(Equation 8) $$TMR = \dot{V}_{O_2} + ANMR \quad \text{mls./min.}$$

(4) PERCENTAGE ANAEROBIC METABOLISM (%ANM) is that portion of total energy expenditure which is being provided by anaerobic processes.

(Equation 9) $$\% ANM = \frac{ANMR}{TMR} \times 100\ \%$$

(5) 95% CONFIDENCE LIMITS for the measured variables were calculated on the basis of the errors involved in each of the technical measurements, as outlined in the appendix. These limits were then employed in estimating the 95% confidence ranges of the derived values.

RESULTS

1. CHARACTERISTICS OF THE PATIENTS

The clinical characteristics of the six patients selected for this study are summarized in table I and their laboratory features, pre- and post-training, in tables II, III, and IV. The mean age of the subjects was 61 years with an age range of 52 - 69 years. The predominant symptom in all cases was dyspnea of exertion severely limiting exercise tolerance. The duration of marked dyspnea ranged from two to nine years, with a mean of 5.5 years. With exception of patients 3 and 5, all had evidence clinically or electrocardiographically of cor pulmonale and right sided heart failure and were taking maintenance digitalis medication. In no cases was there evidence of coronory artery disease or left heart failure.

Analysis of arterial blood at rest (table II) revealed oxygen saturations averaging 86%. Hypercapnea was present in all subjects except 3 and 6, with the group mean pCO_2 measuring 45 mm. Hg. However, this chronic respiratory acidosis was well compensated, the mean arterial pH being 7.39. It is of considerable interest that none of the arterial blood parameters at rest were affected by training, the mean values post-training being either unchanged or insignificantly changed.

Analysis of tables III and IV reveals marked pulmonary dysfunction in all patients with evidence of hyperinflation (mean residual volume of 52%), poor diffusing capacity (mean of 6.6 cc/min/mm.Hg.), reduced maximum

TABLE I

CLINICAL FEATURES OF PATIENTS STUDIED

PT.	AGE	B.S.A.*	CLINICAL FEATURES	CARDIAC STATUS	E.C.G.
1. W.B.	57	1.70	Productive cough and dyspnea 2 yrs.	History rt. heart failure. On Digitalis	P pulm. Rt. axis dev.
2. D.E.	52	1.80	Dyspnea and recurrent infections 8 yrs.	History rt. heart failure. On Digitalis	P pulm. Incomplete RBBB
3. A.M.	61	1.70	Dyspnea and productive cough 4 yrs.	No evidence heart disease	Normal
4. J.S.	69	1.90	Dyspnea and productive cough 5 yrs.	History rt. heart failure. On Digitalis	Rt. vent. hyper. Rt. axis dev.
5. D.R.	62	1.65	Dyspnea 5 yrs. Productive cough 20 yrs.	No evidence heart disease	Non specific ST and T wave changes
6. R.M.	66	1.70	Dyspnea and productive cough 9 yrs.	History rt. heart failure. On Digitalis	Normal
Mean	61		Dyspnea 5.5 yrs.		

* Body Surface Area ($M.^2$)

TABLE II

ANALYSIS OF RESTING ARTERIAL BLOOD PRE- AND POST-TRAINING

PT.	pO_2 mm. Hg.		pCO_2 mm. Hg.		pH		O_2Sat. %	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1. W.B.	60	59	49	44	7.37	7.38	88	87
2. D.E.	46	50	46	48	7.35	7.37	79	83
3. A.M.	74	72	36	37	7.42	7.42	94	93
4. J.S.	54	57	47	47	7.39	7.38	86	87
5. D.R.	40	48	50	53	7.39	7.34	75	79
6. R.M.	73	50	39	45	7.42	7.40	93	84
Mean	58	56	45	46	7.39	7.38	86	86

TABLE III

PULMONARY FUNCTION STUDIES PRE- AND POST-TRAINING

PT.	Vital Capacity*		Total Lung Capacity*		Residual Volume **		$F.E.V._{1.0}$***	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1. W.B.	77	71	99	106	46	53	33	33
2. D.E.	75	85	103	113	50	48	26	26
3. A.M.	77	85	109	116	53	49	36	32
4. J.S.	83	61	125	130	50	64	16	23
5. D.R.	72	67	125	131	57	61	29	25
6. R.M.	65	62	97	99	54	56	25	18
Mean	75	72	110	116	52	55	28	26

* % of Predicted
** % of Total Lung Capacity
*** % of Forced Vital Capacity

TABLE IV

PULMONARY FUNCTION STUDIES PRE- AND POST-TRAINING

PT.	Diffusing Capacity*		Max. Breathing Capacity**		Mixing Efficiency**	
	Pre	Post	Pre	Post	Pre	Post
1. W.B.	6.2	6.3	30	31	39	48
2. D.E.	6.9	-	21	33	32	50
3. A.M.	7.8	7.8	55	50	20	32
4. J.S.	-	4.8	27	26	38	38
5. D.R.	3.6	-	25	29	59	-
6. R.M.	8.3	6.0	23	19	33	19
Mean	6.6	6.2	30	31	37	37

* Steady State Method[6] (cc/min/mm.Hg.)

** % of Predicted

breathing capacity (mean of 30% of normal), inefficient mixing in the lungs (mean of 37% of predicted), and expiratory obstruction (mean $FEV_{1.0}$ of 28% FVC). These findings are all highly characteristic of obstructive pulmonary emphysema. Again, it is of interest that there were no significant changes in any of the parameters of pulmonary function following the training programme, a fact also noted by other investigators.[8,58,66]

2. EVIDENCE OF TRAINING

Since the object of this study was to assess the effects of physical training on the aerobic and anaerobic metabolic rates of patients with emphysema, it was deemed necessary to establish that physical training had in fact occurred. Further, it was felt that the criteria of training would have to be based on the training programme itself rather than on the results of the pre and post-training exercise assessments, since to establish criteria based on the latter would in essence be begging the question and would obviate the necessity of studying the effects of training on metabolic rates.

In table V are summarized the initial and final treadmill walking speeds of each subject along with the corresponding pulse rates immediately following a ten minute walk and two minutes following the walk. It will be seen that the mean starting speed of the oxygen-breathing group (1.5 MPH) was almost identical to that of the air-breathing group (1.4 MPH). However, the increase in speed over the three weeks averaged 1.2 MPH in the first group (an increment of 80%), and 0.6 MPH in the second group (an increment

TABLE V

WALKING SPEED, WALKING PULSE, PULSE 2 MIN. POST-WALK AT INITIATION AND COMPLETION OF TRAINING PROGRAMME

PT.	Gas	Walking Speed M.P.H.		Walking Pulse		Pulse 2 Min. Post-Walk	
		Init.	Final	Init.	Final	Init.	Final
1. W.B.	O_2	1.1	2.4	76	84	76	86
2. D.E.	O_2	1.8	2.6	92	84	81	82
3. A.M.	O_2	1.6	3.0	92	94	87	82
Mean		1.5	2.7	87	87	81	83
4. J.S.	Air	1.3	1.9	77	79	62	68
5. D.R.	Air	1.2	1.8	94	90	77	84
6. R.M.	Air	1.6	2.3	119	108	108	88
Mean		1.4	2.0	97	92	82	80
Mean of 6		1.4	2.3	92	90	82	82

TABLE VI

OXYGEN CONSUMPTION ($\dot{V}O_2$) WITH 95% CONFIDENCE RANGE PRE- AND POST-TRAINING

Patient	Gas	$\dot{V}O_2$ ml/min./M2/100 Kg-M		
		Pre	Post	Change
1. W.B.	O_2	258 ± 4.5	235 ± 4.5	-23
2. D.E.	O_2	285 ± 4.0	256 ± 4.0	-29
3. A.M.	O_2	172 ± 4.0	222 ± 4.0	+50
Mean		238 ± 4.0	238 ± 4.0	-0.7
4. J.S.	Air	162 ± 3.0	357 ± 4.0	+195
5. D.R.	Air	226 ± 3.5	175 ± 3.5	-51
6. R.M.	Air	207 ± 4.0	191 ± 3.5	-16
Mean		198 ± 3.5	241 ± 3.5	+42
Mean of 6		218 ± 4.0	236 ± 4.0	+18

of 43%), the overall increase averaging 0.9 MPH (an increment of 64%). This latter increase in speed is statistically significant ($P < .01$), as is the increase in the O_2 group ($P < .02$) and in the air group ($P < .05$). Also, the difference in mean increases between the two groups is significant ($P < .05$).

Despite these significant increases in walking speeds in all subjects, it will be noted that the mean pulse rates at the faster speeds, both at the end of a walk and two minutes later, were unchanged from those corresponding to the initial slower speeds. Thus, for the same pulse rate subjects were able to walk significantly faster at the completion of the training programme. The significance of this phenomenon will be discussed later.

3. AEROBIC METABOLIC RATE (AMR) ($\dot{V}O_2$)

The aerobic metabolic rates (i.e. oxygen consumption per minute) during the pre- and post-training exercise assessments of each subject are summarized in table VI. In order to make valid comparisons between the pre- and post-training results and among the various individuals, the absolute oxygen consumptions have been brought to a common denominator based on body surface area and work load. Accordingly, the aerobic metabolic rate is expressed in ml./min./M^2/100 Kg M., thus removing any differences due to body weight or unequal bicycle loads.

It will be seen that with the exception of subjects 3 and 4 the oxygen consumption during exercise decreased following training. However,

primarily because of the large increase in $\dot{V}O_2$ of subject 4, there was a statistically insignificant increase of 18 ml./min. in the mean $\dot{V}O_2$ of the entire group.

4. TOTAL BODY EXCESS LACTATE

In figures 1 - 6, adapted from Huckabee,[44] are depicted the changes in total body lactate and pyruvate during exercise and recovery, pre- and post-training, converted to the equivalent number of mls. of oxygen. The curve (Ln-Lo) represents the changes in total body lactate. The shape of the curve (Pn-Po) $\frac{Lo}{Po}$ depicts the relative changes in total body pyruvate and its height indicates the quantity of lactate present solely as a result of changes in pyruvate. This much lactate accumulation must be attributed to changes in ventilation, epinephrine secretion, and glucose metabolism, but not to tissue hypoxia. The remainder of lactate in excess of this must be ascribed to tissue hypoxia and anaerobic glycolysis, and is plotted as total body excess lactate (XL). It will be noted that the curve XL is the algebraic difference between curves (Ln-Lo) and (Pn-Po)$\frac{Lo}{Po}$. Conversely, summing of non-hypoxic lactate, (Pn-Po)$\frac{Lo}{Po}$, and hypoxic lactate, XL, results in total lactate (Ln-Lo).

It should be noted that the curves in figures 1 - 6 represent total body accumulations at various times during exercise and recovery. The blood lactate and pyruvate values from which the total body values were

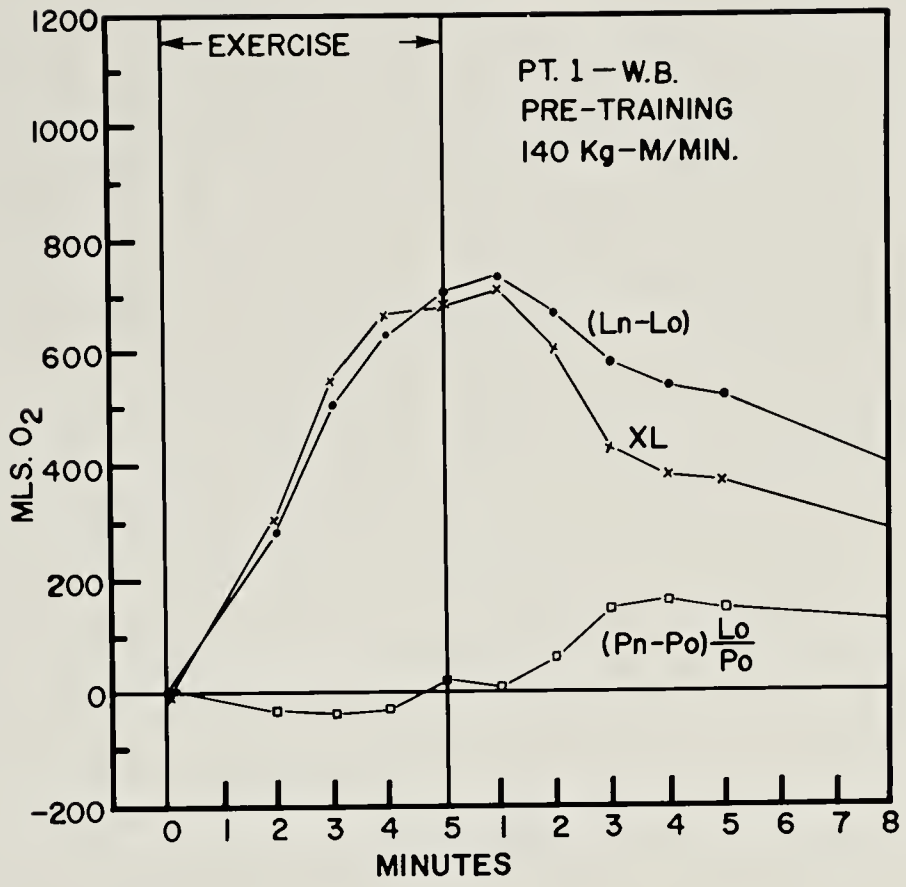


Figure 1 A

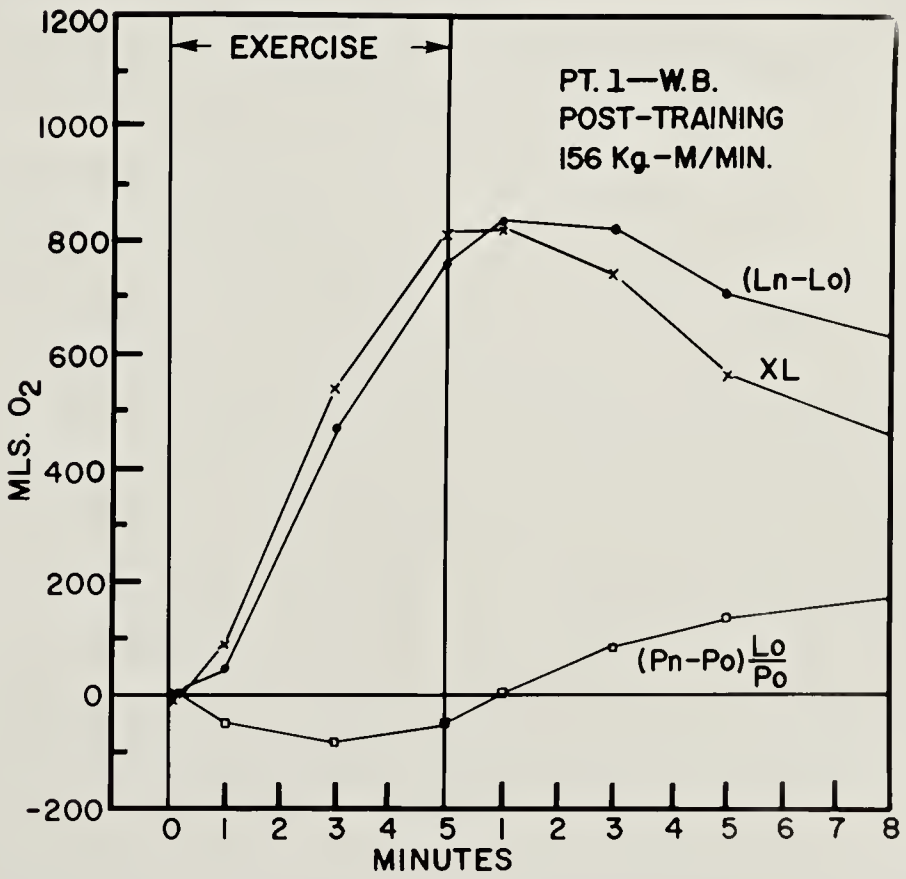


Figure 1 B

Total Body Lactate (Ln-Lo), Excess Lactate (XL) and Non-hypoxic Lactate $(Pn-Po)\frac{Lo}{Po}$, During Exercise and Recovery, Pre- and Post training.

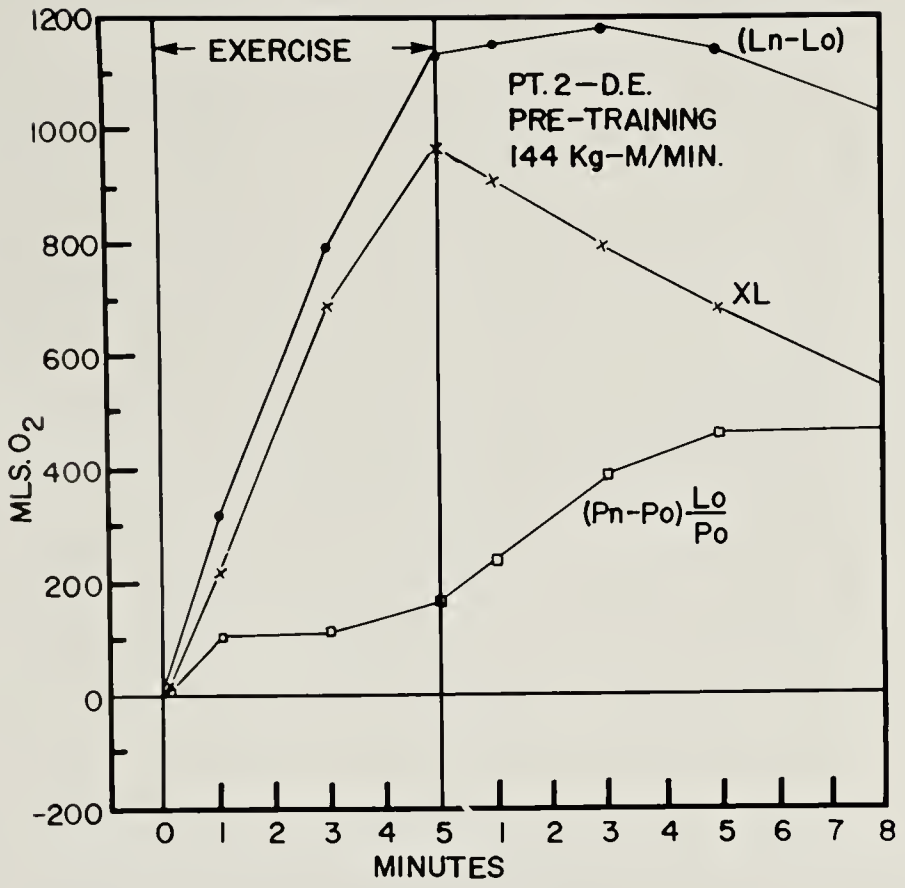


Figure 2 A

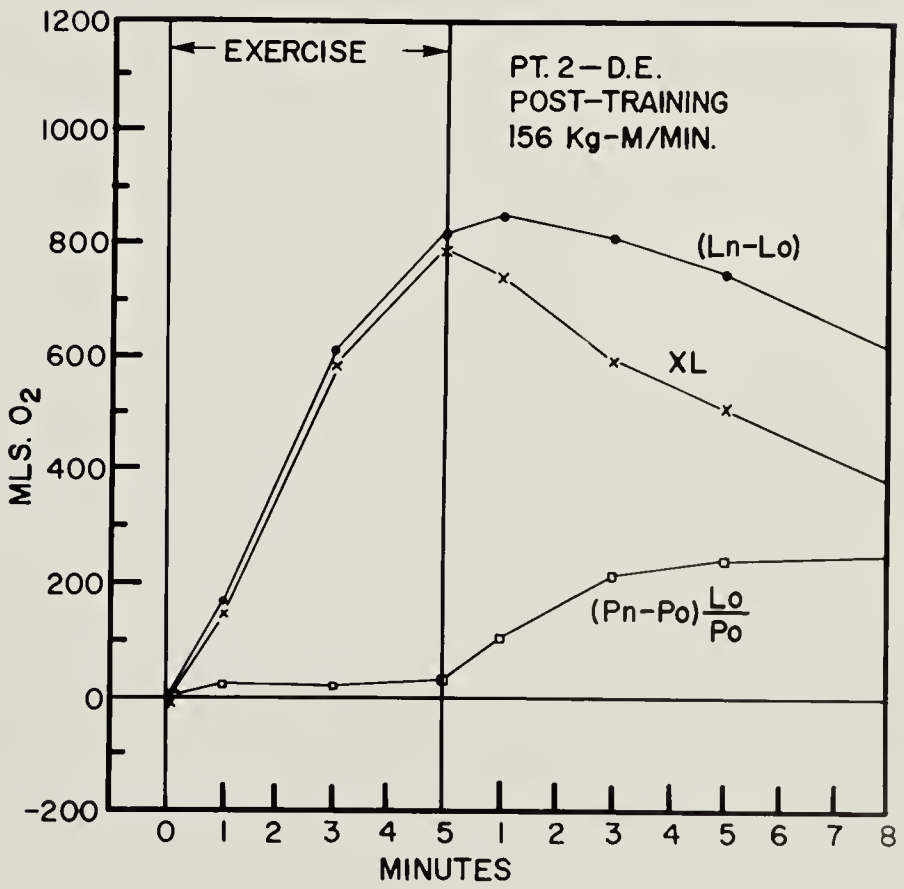


Figure 2 B
Total Body Lactate (Ln-Lo), Excess Lactate (XL) and Non-hypoxic Lactate $(Pn-Po)\frac{Lo}{Po}$, During Exercise and Recovery, Pre- and Post-training.

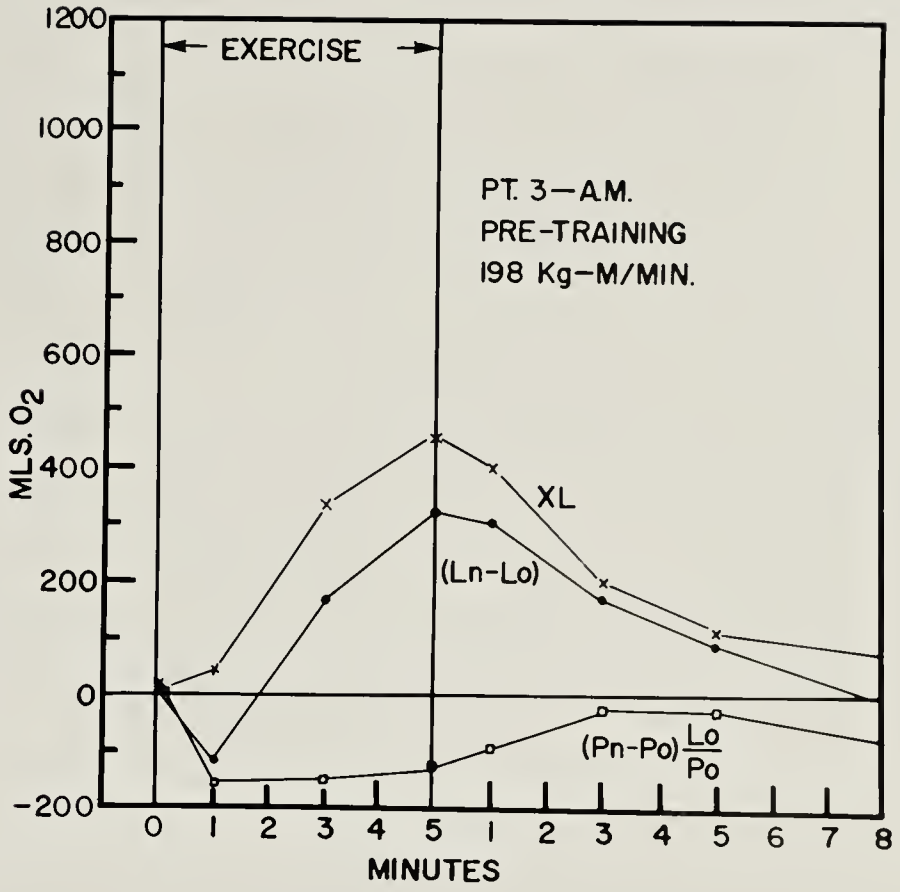


Figure 3 A

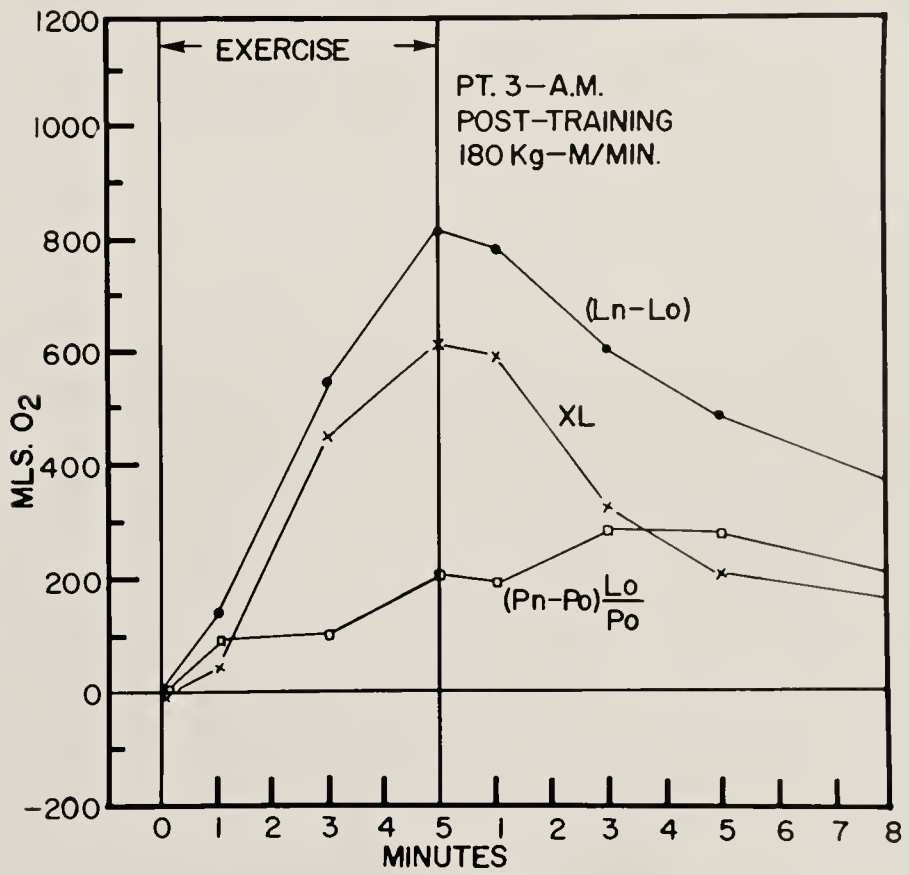


Figure 3 B
Total Body Lactate (Ln-Lo), Excess Lactate (XL) and Non-hypoxic Lactate (Pn-Po)$\frac{Lo}{Po}$, During Exercise and Recovery, Pre- and Post-Training.

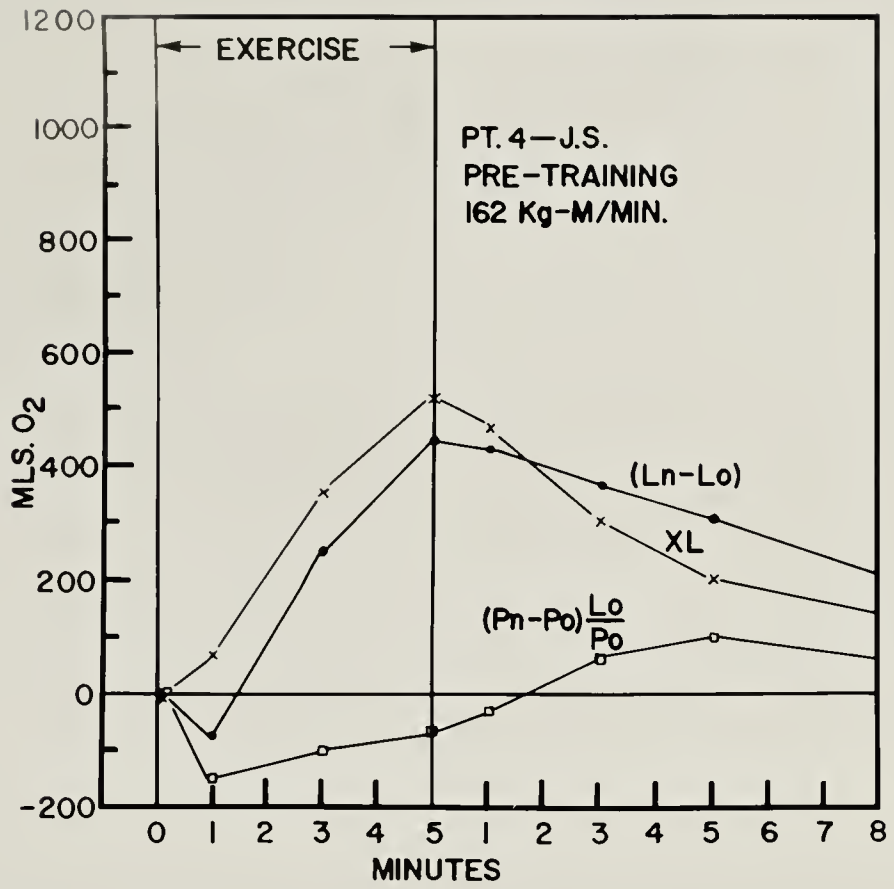


Figure 4 A

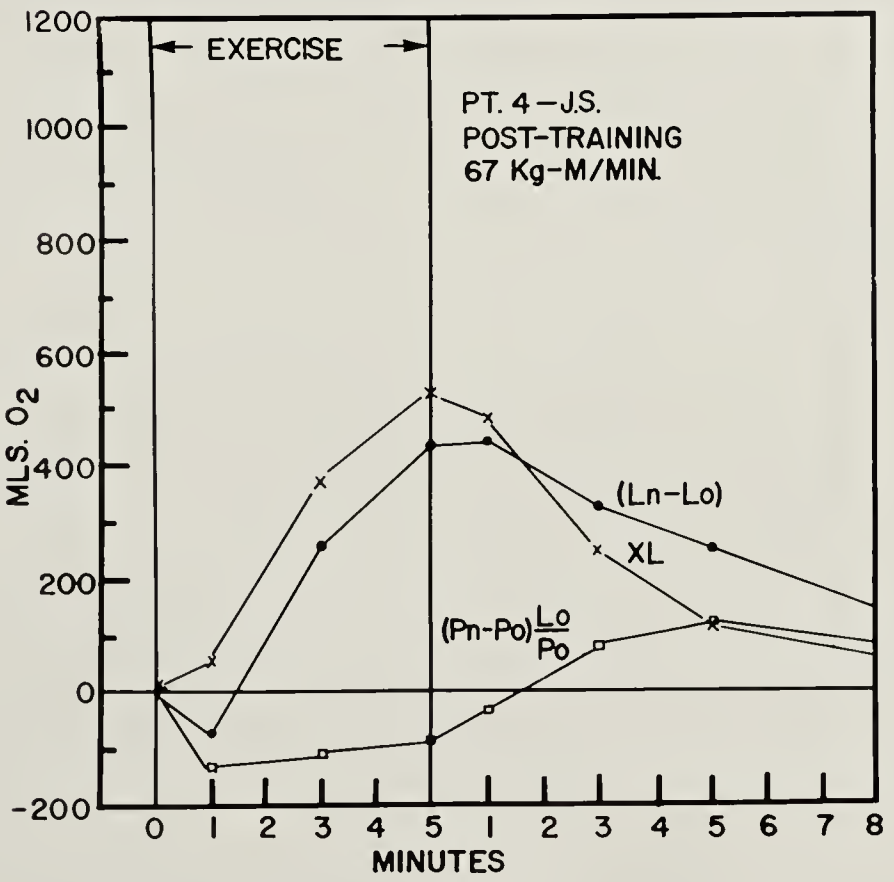


Figure 4 B

Total Body Lactate (Ln-Lo), Excess Lactate (XL) and Non-hypoxic Lactate $(Pn-Po)\frac{Lo}{Po}$, During Exercise and Recovery, Pre- and Post-Training.

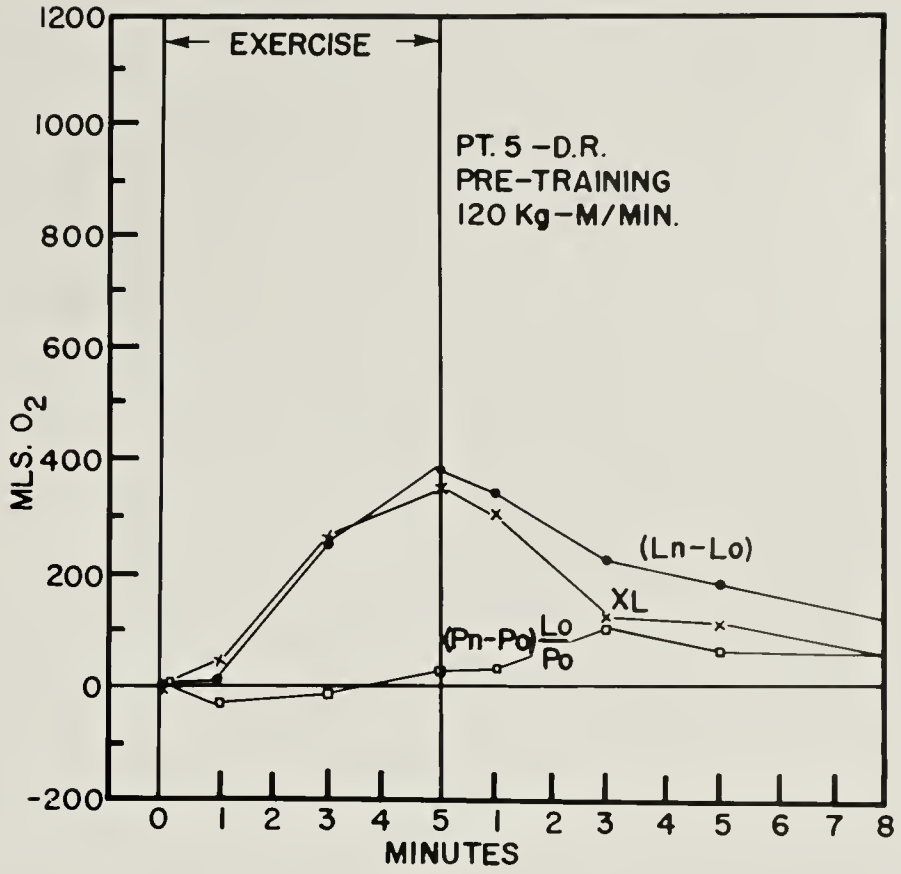


Figure 5 A

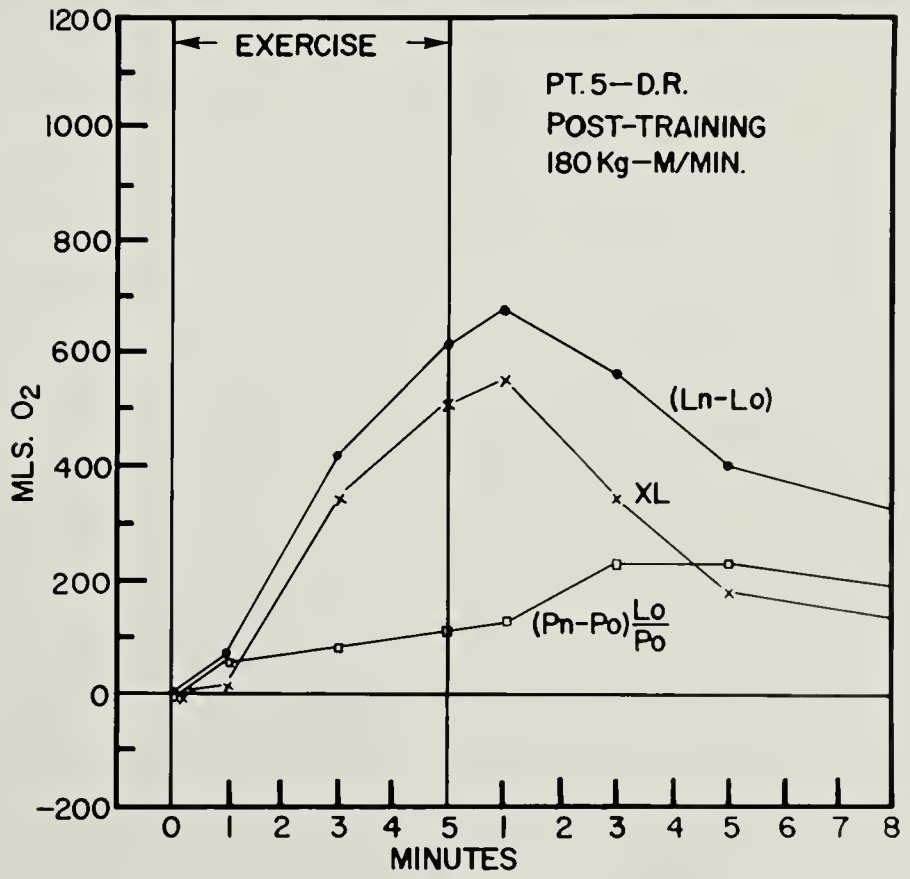


Figure 5 B
Total Body Lactate (Ln-Lo), Excess Lactate (XL) and Non-hypoxic Lactate (Pn-Po)$\frac{Lo}{Po}$,
During Exercise and Recovery, Pre- and Post-Training.

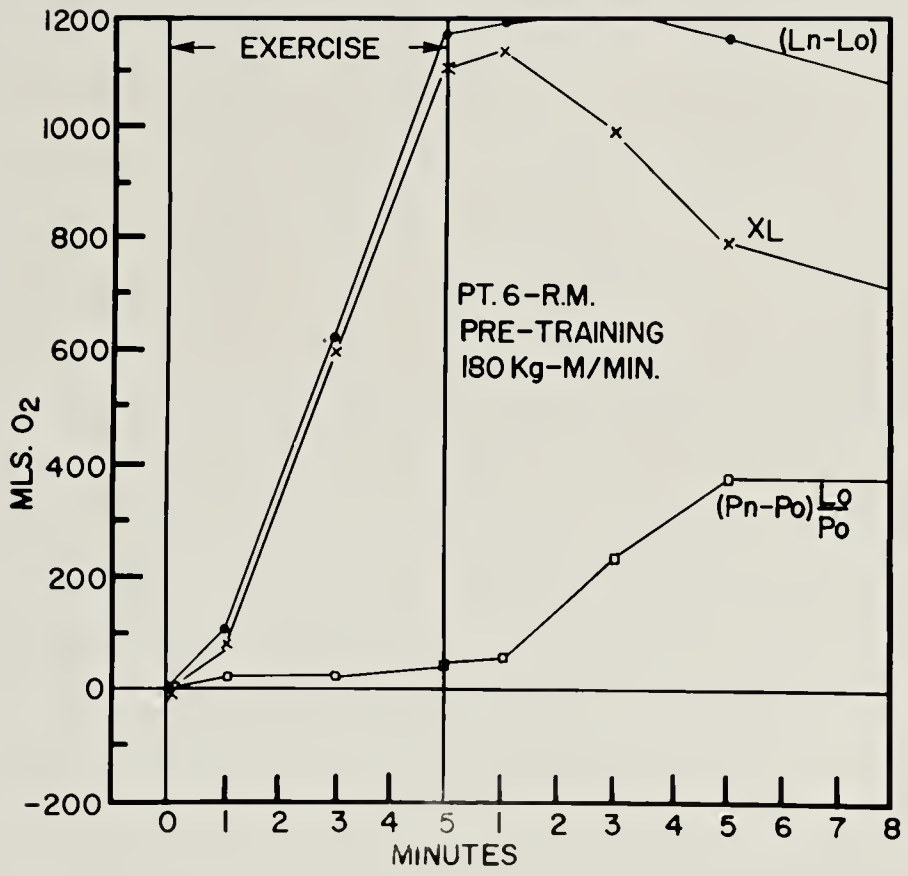


Figure 6 A

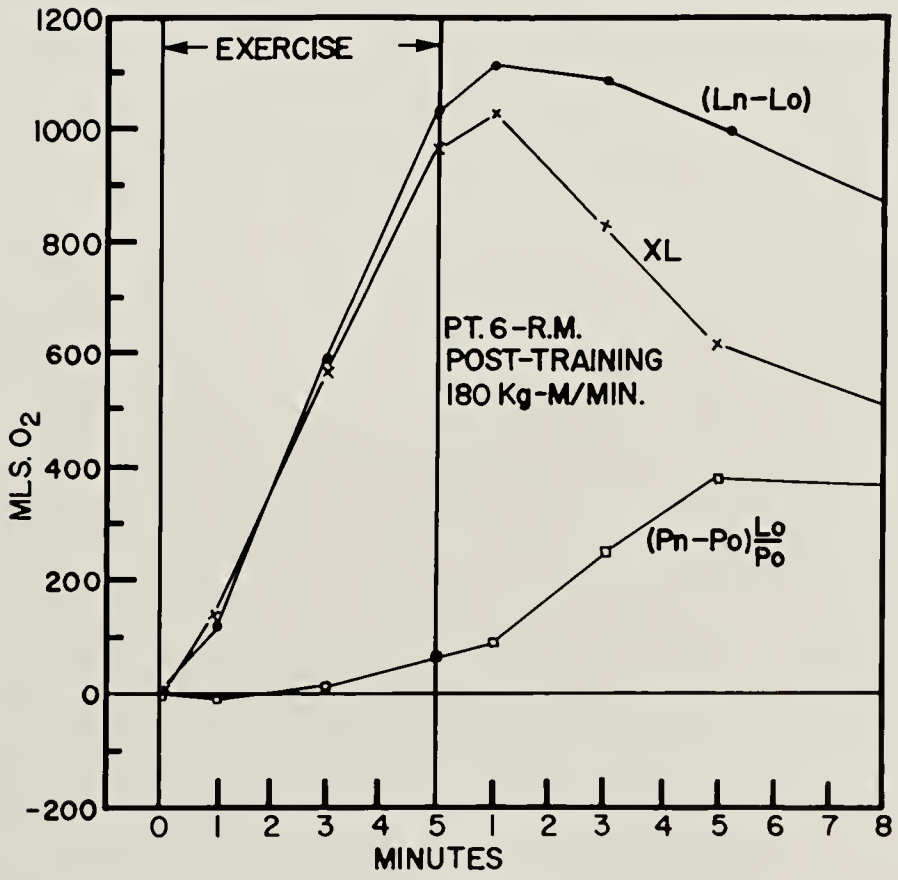


Figure 6 B

Total Body Lactate (Ln-Lo), Excess Lactate (XL) and Non-hypoxic Lactate $(Pn-Po)\frac{Lo}{Po}$, During Exercise and Recovery, Pre- and Post-Training.

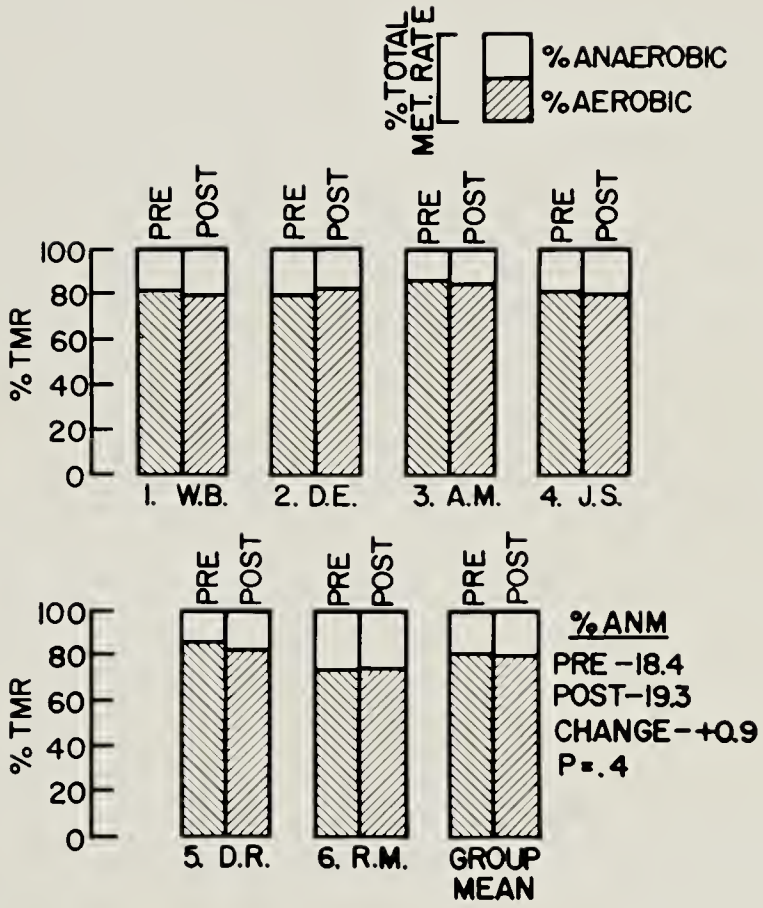


Figure 7

Changes in Percent Anaerobic Metabolism with Training.

calculated are tabled in the appendix. Of importance is the fact that these curves have not been reduced to equal work loads. Therefore, the height of the various curves may differ in the same subject on the pre- and post-training assessments solely as a result of unequal work loads. Of interest however is the fact that the pre- and post-training curves for any given individual are very similar in shape, the curves of patient 3 being the only exception. The significance of this similarity will be discussed subsequently.

5. ANAEROBIC METABOLIC RATE (ANMR)

Table VII summarizes the anaerobic metabolic rates prevailing during exercise for each subject, pre- and post training. As outlined under methods and procedures, (equation 7), the anaerobic metabolic rate is the rate of accumulation of total body excess lactate -- i.e. ANMR = $\frac{dXL_T}{dt}$. As can be seen in figures 1 - 6, the curves of excess lactate accumulation were approximately straight lines. This implies a constant rate of XL accumulation during exercise -- i.e. a constant ANMR -- and hence the slope of these lines, $\Delta XL_T/\Delta t$ is the anaerobic metabolic rate. The latter therefore were calculated by dividing the total body excess lactate present at the end of exercise by the number of minutes of exercise. The resulting figures were then reduced to a common denominator based on body surface area and work load, identical to that used for the aerobic metabolic rate. Therefore, aerobic and anaerobic metabolic rates are expressed in the same units -- ml. of O_2/min./M^2/100 Kg M.

TABLE VII

ANAEROBIC METABOLIC RATE (ANMR) WITH 95% CONFIDENCE RANGE PRE- AND POST-TRAINING

Patient	Gas	ANMR ml/min./M^2/100 Kg-M		
		Pre	Post	Change
1. W.B.	O_2	59 ± 6.5	63 ± 6.0	+4
2. D.E.	O_2	74 ± 7.5	56 ± 6.0	-18
3. A.M.	O_2	27 ± 4.0	38 ± 6.0	+11
Mean		53 ± 6.0	52 ± 6.0	-1
4. J.S.	Air	34 ± 4.0	82 ± 10.5	+48
5. D.R.	Air	36 ± 8.0	37 ± 6.0	+1
6. R.M.	Air	75 ± 4.5	67 ± 5.0	-8
Mean		48 ± 5.5	62 ± 7.0	+14
Mean of 6		51 ± 6.0	57 ± 6.5	+7

It will be noted in table VII that the only large increases in anaerobic metabolic rate during exercise following training occurred in subjects 3 and 4, the same subjects whose aerobic metabolic rates increased following training. In the remaining four patients there was either a moderate decrease or a small increase in anaerobic metabolic rate following training. The changes in this parameter when the entire group was considered as a whole are not statistically significant ($P > .5$).

6. TOTAL METABOLIC RATE (TMR)

The total metabolic rate of exercise is the sum of the aerobic and anaerobic metabolic rates of exercise and represents the total amount of energy expended in performing work. The total metabolic rates are summarized in table VIII for the pre- and post-training exercise assessments. It will be noted that in four subjects the TMR of exercise decreased significantly with training ($P < .05$), but due to large increases in the TMR of subjects 3 and 4, the overall change of 24 ml./min. is not significant.

7. PERCENT ANAEROBIC METABOLISM (%ANM)

The percentage of total energy expenditure which was being provided by anaerobic processes during exercise is equal to (ANMR $\div$ TMR) x 100. These percentages, pre- and post-training, are listed in table IX and depicted in figure 7. It is of considerable interest that despite the various changes

in $\dot{V}O_2$, ANMR, and TMR which occurred with training, the fraction of energy provided anaerobically during exercise was completely unaltered. It will be noted that all the recorded changes in % ANM are within the 95% confidence limits of the parameter and are of no significance ($p = .4$). The implications of this finding will be discussed later.

TABLE VIII

TOTAL METABOLIC RATE (TMR) WITH 95% CONFIDENCE RANGE PRE- AND POST-TRAINING

Patient	Gas	TMR ml/min./M^2/100 Kg-M.		
		Pre	Post	Change
1. W.B.	O_2	317 ± 11.0	298 ± 10.5	-19
2. D.E.	O_2	359 ± 11.5	312 ± 10.0	-47
3. A.M.	O_2	199 ± 8.0	260 ± 10.0	+61
Mean		292 ± 10.0	290 ± 10.0	-2
4. J.S.	Air	196 ± 7.0	439 ± 14.5	+243
5. D.R.	Air	262 ± 11.5	212 ± 9.5	-50
6. R.M.	Air	282 ± 8.5	258 ± 8.5	-24
Mean		247 ± 9.0	303 ± 11.0	+56
Mean of 6		269 ± 9.5	293 ± 10.5	+24

TABLE IX

PERCENT ANAEROBIC METABOLISM (%ANM) WITH 95% CONFIDENCE RANGE PRE- AND POST-TRAINING

Patient	Gas	% ANM		
		Pre	Post	Change
1. W.B.	O_2	18.7 (16.7 - 20.6)	21.1 (19.2 - 23.0)	+2.4
2. D.E.	O_2	20.7 (18.7 - 22.7)	18.0 (16.1 - 19.9)	-2.7
3. A.M.	O_2	13.6 (11.5 - 15.6)	14.7 (12.4 - 17.0)	+1.1
Mean		17.7	17.9	+0.2
4. J.S.	Air	17.3 (15.2 - 19.3)	18.7 (16.7 - 20.8)	+1.4
5. D.R.	Air	13.7 (10.8 - 16.4)	17.5 (14.8 - 20.1)	+3.8
6. R.M.	Air	26.5 (24.9 - 28.1)	26.0 (24.1 - 27.8)	-0.5
Mean		19.2	20.7	+1.6
Mean of 6		18.4	19.3	+0.9

DISCUSSION

1. EVIDENCE OF TRAINING

A prerequisite to discussion of the effects of physical training on the anaerobic and aerobic metabolic rates of exercise is evidence that physical training has in fact occurred. It has already been pointed out that analysis of arterial blood and of pulmonary function, at rest, revealed no significant changes to have taken place as a result of training. That tests of pulmonary function in emphysema patients are unaltered by training and breathing exercises has been noted by Becklake,[8] Pierce,[66] and Miller.[58] The lack of improvement is not surprising in that the abnormalities of function in such patients arise primarily as a result of irreversible anatomical disruptions in the pulmonary parenchyma and airways. Such pathology could hardly be expected to change consequent to physical exercise. Since to a large extent the abnormalities in blood gas composition are secondary to the disordered pulmonary physiology, the absence of improvement in arterial pO_2, pCO_2, and O_2 saturation is also understandable.

Accordingly, proof of training must be established from studies of other parameters. As pointed out previously, use of the response to exercise in terms of metabolic rates would be incorrect for this purpose. Therefore, the fact that training did occur was assumed in view of the significant increase in walking speed which occurred in all subjects during the course of the

training programme without any corresponding increases in the pulse rate. Such a decrease in the physiological stress involved in work is generally accepted as a sign of training.[58,66,67] Nevertheless, it cannot be stated conclusively that this apparent improvement was the result of physiological training rather than mere practice and familiarity with the treadmill, although treadmill practice has been reported not to occur,[24] presumably because of the virtually identical nature of the exercise to ordinary floor walking.[72]

2. ENERGY COST OF EXERCISE - EFFECTS OF TRAINING

A decrease in the energy cost of exercise following training is the sinequanon of increased muscular efficiency and improved physical fitness.[21,49] That such an economy of energy expenditure develops with training is a well documented fact, particularly in healthy subjects[49,71] but also in patients with obstructive emphysema.[58,66,67] The degree of this improvement is generally assessed by measuring the oxygen cost of a given work load. Since normal subjects supply 95% or more of their energy requirements aerobically during mild to moderate exercise,[44,50] conclusions based on oxygen consumption alone are reasonably valid. Where disturbances in oxygen delivery to the muscles exist, and a significant fraction of energy is provided by anaerobic mechanisms, it is obvious that no conclusions based on oxygen consumption alone are justified. Indeed, it is conceivable that training of such a patient may

increase the anaerobic capacity and tolerance in such a way as to decrease the demands placed upon the impaired cardiorespiratory system for oxygen without producing any decrease in the combined aerobic and anaerobic cost of exercise.

It is of considerable interest therefore that analysis of the $\dot{V}O_2$, ANMR, and TMR of these six patients with emphysema (tables VI-VIII) reveals decreases in the energy cost of exercise to have occurred with training in patients 1,2,5 and 6, the decreases being manifested both in the aerobic and anaerobic components of energy production. In two subjects, however, 3 and 4, there was an increase in the total metabolic rate of exercise following training. This change included increases in both the aerobic and anaerobic components of energy production, and occurred despite the evidence of training discussed previously -- i.e. faster walking speed with no increase in pulse rate.

An explanation for the apparent deterioration of subjects 3 and 4 must be offered. A simple explanation might be that of technical errors of measurement. However, since there is no interdependence between the measurements of oxygen consumption and excess lactate accumulation, it is highly unlikely that large errors in the same direction would be made coincidentally in the two parameters. This fact, plus the magnitude of the increases noted, mitigates against technical error as the basis for the findings. Similarly, to conclude that perhaps the two subjects may not in

fact have been trained is also unjustified. In fact, the largest increase in walking speed of the six subjects occurred in patient number 3, without any apparent alteration in heart rate.

It is evident therefore that the increased energy expenditure noted during the post-training assessment could not have been on the part of the muscles which had been trained -- the back, thigh, and leg muscles -- and must have been utilized by other tissues, in all likelihood the muscles of respiration.

The manifestations of chronic obstructive emphysema commonly show day to day variation coincident with changes in bronchial secretions and tone and airway patency. Since the work of breathing is known to be increased in obstructive pulmonary disease,[13] it is quite plausible that a sudden further increase in the energy expenditure of the respiratory muscles occurred in subjects 3 and 4 during their post-training assessments, accounting for the large increment in aerobic and anaerobic metabolic rates over the pre-training values. Such an increase in work of breathing may have been the result of inspissated bronchial secretions or of some degree of bronchospasm. It is worth noting in this regard that subjects 3 and 4 appeared to be severely dyspneic during their post-training assessments. Subject 4 in fact required that the work load be decreased considerably from the pre-training level. If, as postulated, the energy requirements of the respiratory muscles had sharply

increased, energy available to perform external work -- i.e. to drive the bicycle -- would be severely limited and would necessitate a reduction in work load.

3. THE ANAEROBIC METABOLIC RATE IN EMPHYSEMA

As noted in table IX, the anaerobic metabolic processes of these six subjects supplied from 13 to 26% of the total energy requirements during mild to moderate exercise. This compares with values of 5% or less in healthy subjects.[44,50,75] The only studies of this nature reported in disease states have been in cardiac patients, where anaerobic glycolysis has been noted to supply 20 - 50% of the energy requirements for mild work.[44,75]

Before any absolute correlation can be made between disease processes and anaerobic metabolic rates, it seems necessary to establish that there is no natural increase in the % ANM with age. This is particularly true in the present study where the mean age of the subjects was 61 years, whereas most studies of normals were done in much younger subjects. In this regard it has been demonstrated that the maximum aerobic capacity [2,23] and heart rate[3] attainable during severe exercise decrease with age, but the response to moderate, submaximal work loads reveals no significant reductions in oxygen consumption or heart rate in subjects under the age of seventy.[1,2,52] Further, the relationships between heart rate and blood lactate, work load and excess lactate, and oxygen consumption and excess lactate have been found

to be unaffected in normal subjects by increasing age.[2,74]

In view of these findings, the 13-26% of energy requirements supplied anaerobically by the patients of this study can justifiably be attributed to the disease processes from which they were suffering. Since anaerobic processes are evidently utilized to any significant degree only when the delivery of oxygen to tissues is insufficient to meet demands, it is logical to conclude that the high index of anaerobiosis noted in this study is the result of impairment of the pulmonary or circulatory response to stress, or both. All of the subjects herein manifested marked respiratory dysfunction and difficulties in oxygenating blood, even at rest. As pointed out previously, these defects become magnified during exercise. In addition, four of the subjects had clinical evidence of right-sided congestive failure which has been demonstrated to lead to higher than normal anaerobic glycolysis even in well compensated individuals during mild exercise.[44] It will be noted that the two subjects of this study without signs of heart disease, 3 and 5, had the lowest % ANM during exercise, both before and after training. It would seem reasonable to attribute their increased call on anaerobic processes primarily to pulmonary impairment, whereas a combination of pulmonary and cardiac defects probably accounted for the still higher % ANM in the other four patients.

4. % ANM - THE EFFECT OF TRAINING

As noted in table IX, the percentage of energy requirements supplied anaerobically during exercise was unaffected by physical training. This is particularly noteworthy in view of the fact that the total energy expenditure during exercise was altered in all subjects (table VIII), decreasing in four and increasing in two, with corresponding changes in the absolute aerobic and anerobic metabolic rates (tables VI, VII). Despite all these changes, the ratio of anaerobic to aerobic metabolism remained constant. The effects of training on this ratio have not been reported in the medical literature for any pathological states, but indirect assessments based on the post-exercise oxygen debt tend to suggest that decreases in the anaerobic and increases in the aerobic components of energy production occur with training.[66] That these anticipated changes did not occur, particularly in view of the evidence of training in all subjects (table V) and of increased muscular efficiency in four subjects (table VIII), is difficult to explain. The implication is that despite a reduction in the total energy cost of a given exercise consequent upon training, the cellular "biochemical thermostat" is set at a certain ratio of aerobic to anaerobic peculiar to each patient and is completely unaffected by training.

There is animal evidence,[20,47] although far from conclusive, which suggests that cardiac output is regulated to some degree under hypoxic

conditions by an unidentified circulating metabolite. Since the most important byproduct of tissue hypoxia is excess lactate, the latter has been implicated.[20] It is plausible therefore to speculate that were there a tendency for less anaerobic metabolism to occur with training, the amount of circulating excess lactate would decrease. If excess lactate is indeed a stimulus to cardiac output, the latter would fall with the reduction in excess lactate. In the face of a diminished cardiac output oxygen delivery to the tissues would in turn decrease, leading to a lower aerobic metabolic rate. If the decreases in anaerobic and aerobic metabolic rates were of the same order, their ratio would be unaltered and the % ANM would remain constant despite an overall reduction of energy expenditure.

5. THE BEHAVIOR OF LACTATE, PYRUVATE, AND EXCESS LACTATE

Comment has already been made of the fact that the patterns of total body lactate, pyruvate, and excess lactate accumulation (figures 1-6) for any given subject are essentially unaltered in shape following training. The explanation for this phenomenon may very likely rest with the "biochemical thermostat" alluded to previously. It is conceivable that the constancy of the relationship among these interdependent metabolites is part of the biochemical regulatory mechanism which maintains the unchanging ratio of anaerobic to aerobic metabolism. Just as the absolute levels of the metabolic rates may change with training, but always in the same proportion, so it would

appear to be with lactate, pyruvate, and excess lactate.

A great deal of controversy exists in the medical literature with regard to the concept of a constant anaerobic metabolic rate during exercise. Huckabee[43] was the first to provide evidence of a direct nature, based on excess lactate, of a constant anaerobic rate even during mild exercise. The presence of anaerobic metabolism in anything less than severe exercise, and its constancy have both been disputed.[50,55,75] Results of the present study in emphysema patients support the concept of a constant anaerobic rate during even moderate exercise. The results also offer some explanation of the differences between Huckabee and his opponents. Many of the latter used blood lactate per se as the index of anaerobic metabolism and interpreted a lack of lactate rise as evidence of the absence of anaerobic glycolysis. According to the present results, as shown in figures 1-6, there is often a tendency for non-hypoxic lactate, $(Pn-Po)\frac{Lo}{Po}$, to decrease early in the course of exercise, possibly due to changes in blood pH. This pattern is generally found in well-trained individuals of the type usually studied in normal investigations. The absence of a concomitant decrease in total lactate implies the presence of excess lactate and anaerobic metabolism. Thus, in studies which monitor total lactate only and fail to quantitate the amount present as excess lactate, failure of a rise of blood lactate early in exercise may not mean an absence of anaerobic metabolism if in fact the lactate level

should have fallen.

This reasoning may also be invoked to question the existence of an "alactic" oxygen debt, said to be present early in the course of exercise.[53] It is clear that failure of a rise in lactate per se does not rule out the presence of "lactic" anaerobic metabolism, and therefore cannot be said to imply the presence of "alactic" processes.

Despite these considerations, a few studies in normal subjects based on excess lactate rather than merely lactate, do suggest that anaerobic processes play a decreasing role in energy provision as exercise progresses beyond the first few minutes.[50,78] It is commonly accepted that once a "steady state" has been achieved, energy requirements are being met by contemporary oxygen intake. The presence of a constant rate of excess lactate accumulation in the patients of this study, even when oxygen consumption had reached a plateau, implies that a "steady state", in the conventional sense, was never reached. The leveling off of oxygen consumption may have occurred when the limit of the damaged cardio-respiratory apparatus to deliver oxygen was surpassed. More likely, however, oxygen consumption leveled off in accordance with the setting of the "biochemical thermostat", thus sparing the weakened cardio-respiratory system the added stress of supplying more oxygen per minute to the tissues.

It will be noted in figures 1A,5B,6A, and 6B that the curve of excess lactate (XL) continued to rise during the first minute following

cessation of exercise, and in a few others it failed to decrease. This can probably be attributed to the large minute ventilation which occurs during the first one to two minutes of recovery and to the tremendous work involved in supplying this ventilation in subjects whose energy cost of breathing even at rest is higher than normal. In essence, the first minute of recovery was really a part of the exercise, with the work being done by the respiratory muscles.

The shape of the non-hypoxic lactate curves, $(Pn-Po)\frac{Lo}{Po}$, is of interest in that in all cases there was a marked rise in non-hypoxic lactate coincident with a decrease in XL during the recovery process. As pointed out previously, lactic acid is a strong acid, being almost completely ionized at body tissue pH. Carbonic acid in comparison is relatively weak, the respective pK's being 3.86 and 6.10. Accordingly, as excess lactate is oxidized to carbon dioxide and water during the recovery process, there would be a tendency for the pH to rise sharply, particularly since the weaker carbonic acid so formed is removed almost immediately through the lungs. An increase in non-hypoxic lactate, as is seen to occur, would have a buffering effect, thus preventing sudden large shifts in tissue pH.

6. THE EFFECTS OF OXYGEN

Analysis of table V reveals an increase of 1.2 MPH in the mean walking speed to have occurred during the course of training in the three

subjects who breathed oxygen-enriched air. The corresponding increase in the air-breathing group was 0.6 MPH, the difference between the two groups being statistically significant. It is apparent therefore that oxygen enables a patient with emphysema to exercise more strenuously than would otherwise be possible. This fact has been noted previously in somewhat similar investigations.[20,58] It was unknown however whether some basic change in exercise physiology and biochemistry could be achieved as a result of training with oxygen. Speculation on this point led to the hypothesis that perhaps the abundant supply of oxygen being delivered to the tissues would obviate the necessity of calling-forth anaerobic processes of energy production. This in turn, it was felt, might lead to a decreased capacity for anaerobic glycolysis and tolerance to lactic acid which might be detected subsequent to training even when breathing room air.

The fallacy of such reasoning can be demonstrated by analysis of the $\dot{V}O_2$, ANMR, and TMR of these six patients (tables VI - VIII), there being no significant differences in any of these processes between the O_2 group and the air-group; and particularly by analysis of the % ANM (table IX), there being no change in this parameter in either group.

The therapeutic efficacy of oxygen breathing in emphysema cannot be disputed. It is apparent however that the effects of oxygen are present only immediately and that when the delivery of oxygen to cells is subsequently

impaired, anaerobic processes are called forth in a normal manner. Since the tendency for reduced $NADH_2$ to oxidize through the lactic dehydrogenase system rather than through the electron transport system is dependent solely on the immediate availability of oxygen, it is not surprising that the previous inhalation of oxygen-enriched air would have no effect on anaerobic processes prevailing at a later date. Biochemical processes, dependent as they are upon oxidation - reduction potentials and affinities for electrons, can hardly be expected to be "trained" to react differently when the same set of intracellular conditions are present at various times.

It is clear, therefore, that the beneficial effect of oxygen in such patients is derived from its influence on disease processes, rather than from an alteration in the normal processes of cellular physiology and biochemistry.

SUMMARY AND CONCLUSIONS

The purpose of this study was to assess the effects of physical training on the mechanisms of energy production during exercise in patients with chronic obstructive pulmonary emphysema. Accordingly, six male subjects with long-standing and disabling obstructive emphysema were trained for a period of three weeks on a programme of treadmill walking. A second problem was to determine the long-term effects, if any, of breathing oxygen-enriched air as opposed to room air during the training programme. The effects of training on energy production were assessed during exercise on a bicycle ergometer by measuring a number of variables that enabled calculation of aerobic and anaerobic metabolic rate.

On the basis of the results obtained and the implications thereof, the following points can be made:

1) Patients with emphysema respond to physical training in a manner qualitatively similar to that found in normal subjects -- i.e. a decrease in the physiological stress of exercise for a given work load, and an increase in exercise tolerance as evidenced by increased walking ability. It can therefore be suggested that moderate exercise therapy is beneficial in such individuals.

2) The breathing of oxygen-enriched air significantly increases the exercise capacity of patients with emphysema during the period of oxygen administration. Consequently, subjects who may otherwise be incapacitated may be capable of exercising and therefore of training while breathing oxygen.

3) Physical training in emphysema patients appears to reduce the total energy expenditure required to perform a given task. This reduction is most likely a reflection of improved muscular efficiency, but may also be related to decreases in the work of breathing.

4) The fraction of energy requirements provided by anaerobic processes during mild to moderate exercise is considerably higher in emphysema patients than in normal subjects. This pathophysiological response may be attributed to the pulmonary and circulatory deficits present in such patients. It is of interest that the two subjects without evidence of cardiac disease utilized anaerobic processes to a lesser degree than those with combined cardiopulmonary disorders.

5) Despite the apparently beneficial effects of training in reducing the total energy expenditure of exercise, the biochemical mechanisms of energy production are completely unaltered with training, there being no changes in the percentage of anaerobic metabolism. This phenomenon is probably related to the intracellular biochemical and physiological conditions prevailing in the muscles during exercise and is dependent upon physical and chemical laws which are unchanged by training.

6) The breathing of high concentrations of oxygen during a training programme has no long-term effects on the mechanisms of energy production during exercise.

7) Excess lactate appears to be a more reliable index of anaerobic metabolism than lactate per se since the latter includes a non-hypoxic lactate component and does not necessarily follow any predictable pattern of change during exercise or recovery. Conversely, excess lactate has been demonstrated to rise in all subjects during the course of exercise, and to fall during the recovery phase. Although this excess lactatemia does not rule out an "alactic" mechanism of anaerobic metabolism, it does

indicate that "lactic" anaerobiosis is present throughout even mild to moderate exercise. Further, the rate of lactic anaerobic metabolism is relatively constant throughout the exercise period, but conceivably could decrease, as in normal subjects, if exercise is prolonged beyond five minutes.

8) The continued increase of total body excess lactate beyond the point at which oxygen consumption has reached a plateau implies that a "steady-state" in the conventional sense, is not obtained by patients with emphysema even during sub-maximal exercise. The continued accumulation of excess lactate probably contributes to the easy fatiguability, dyspnea, and decreased exercise tolerance manifested by such patients.

APPENDIX

1) RAW DATA

1) EXPIRED AIR volumes and content of O_2 and CO_2 are summarized in tables X - XV. From these data, aerobic metabolic rates ($\dot{V}O_2$) were calculated, as summarized in table VI.

2) BLOOD LACTATE AND PYRUVATE contents are summarized in tables XVI - XXI. From these values total body excess lactate was calculated, as depicted in figures 1-6. The latter was then used in assessing ANMR's, as summarized in table VII.

3) BLOOD WATER CONTENT averaged 0.798 for all subjects. A figure of 0.80 is universally employed for this parameter. Hence the latter value was used for all patients, the resulting error being negligible.

4) BODY WATER CONTENT was calculated according to the formula of Moore.[60,61]

$$100 \times \frac{\text{Total body water}}{\text{Body weight}} = 79.45 - 0.24\ (\text{Body Wt.}) - 0.15\ (\text{Age})$$

The resulting values, used in calculating total body excess lactate, are shown in table XXII.

2) 95% CONFIDENCE LIMITS

1) MEASURED VARIABLES The errors involved in day to day calibration of the O_2 and CO_2 analyzers, and in measuring actual O_2 and CO_2 contents and gas volumes were estimated by repeated analysis of a gas mixture on two different days. Significant day to day calibration errors were eliminated by calculating an F value based on variance ratios.[39] The standard error of the technical measurements was then calculated from which the 95% confidence limits were ascertained as $\pm$ t S.E. $_{\bar{x}}$, the value of t being determined from the probability choice (95%), number of degrees of freedom, and the table of t distributions.[39] The details of these analyses are summarized in tables XXIII - XXV.

In the case of blood lactate and pyruvate, where analyses were done in duplicate on unknown specimens, the method of Copeland[17] was employed to set confidence limits. The standard deviation was calculated utilizing the differences between paired determinations, and the 95% confidence limits determined as three times the standard deviation, although theoretically only twice the standard deviation is required for 95% confidence. The details of this procedure are summarized in tables XXVI and XXVII.

2) DERIVED VARIABLES The 95% confidence ranges of the $\dot{V}O_2$, ANMR, TMR, and % ANM (as shown in tables VI - IX) were calculated utilizing the 95% limits determined for the various measured variables that enter into the derivation of the $\dot{V}O_2$, ANMR, TMR, and % ANM. In so doing the largest possible range that could be obtained for each derived parameter was the one reported in the results.

3) STATISTICAL ANALYSIS

1) DIFFERENCES BETWEEN GROUPS (O_2 breathing and air breathing) were analyzed utilizing the unpaired t-test,[39] based upon the standard error of the difference between the two group means.

$$t = \frac{\text{difference between group means}}{\text{S.E. difference between means}}$$

$$= \frac{\bar{x}\,1 \quad - \quad \bar{x}\,2}{\text{S.E. } \bar{x}\,1 \; - \bar{x}\,2}$$

2) EFFECTS OF TRAINING on any given parameter (walking speed, $\dot{V}O_2$, ANMR, TMR, % ANM) were analyzed utilizing the paired t-test,[39] based upon the differences in that parameter which occurred in each subject with training.

$$\text{Variance} = \frac{\text{E (differences)}^2 - (\text{sum of diff.}) \quad (\text{mean of diff.})}{n - 1}$$

$$\text{S.D.} = \sqrt{\text{variance}}$$

$$\text{S.E.} = \sqrt{\frac{\text{S.D.}}{n}}$$

$$t = \frac{\text{mean of differences}}{\text{S.E.}}$$

TABLE X

ANALYSIS OF EXPIRED AIR PRE- AND POST-TRAINING

PATIENT 1 - W.B.

Mins. of Exercise	$\dot{V}_{E_{STPD}}$ L/min.	% O_2	%CO_2
Pre-training			
Rest	8.06	18.03	2.90
1	8.65	17.50	3.55
2	15.29	17.18	3.85
3	16.63	17.25	4.05
4	16.26	17.25	4.10
5	18.78	17.30	4.10
Post-training			
Rest	7.95	17.30	3.35
1	7.97	17.03	3.55
2	13.58	16.65	4.05
3	14.46	16.65	4.35
4	15.47	16.80	4.35
5	15.39	16.80	4.55

TABLE XI

ANALYSIS OF EXPIRED AIR PRE- AND POST-TRAINING

PATIENT 2 - D.E.

Mins. of exercise	$\dot{V}_{E_{STPD}}$ L/min.	% O_2	% CO_2
Pre-training			
Rest	8.64	17.00	3.60
1	9.07	16.88	3.65
2	-	-	-
3	-	16.23	5.00
4	17.18	16.43	4.90
5	15.67	16.53	4.80
Post-training			
Rest	9.18	17.33	3.40
1	9.61	17.40	3.20
2	16.00	16.95	3.80
3	18.02	17.28	3.50
4	19.92	17.18	3.80
5	19.86	17.20	3.90

TABLE XII

ANALYSIS OF EXPIRED AIR PRE- AND POST-TRAINING

PATIENT 3 - A.M.

Mins. of exercise	$\dot{V}_{E_{STPD}}$ L/min.	% O_2	% CO_2
Pre-training			
Rest	9.63	18.35	2.80
1	15.93	18.10	2.95
2	17.64	17.95	3.20
3	18.60	17.68	3.45
4	18.06	17.85	3.40
5	19.77	17.83	3.45
Post-training			
Rest	8.85	17.83	2.90
1	13.53	17.75	3.00
2	17.07	17.30	3.45
3	20.95	17.58	3.50
4	18.47	17.88	3.20
5	22.30	17.75	3.40

TABLE XIII

ANALYSIS OF EXPIRED AIR PRE- AND POST-TRAINING

PATIENT 4 - J.S.

Mins. of exercise	$\dot{V}_{E_{STPD}}$ L/min.	% O_2	% CO_2
Pre-training			
Rest	9.82	18.30	2.45
1	9.95	18.13	2.55
2	14.14	17.75	2.90
3	16.00	17.83	2.95
4	15.18	17.88	2.90
5	16.60	17.83	3.00
Post-training			
Rest	10.69	18.33	2.65
1	11.69	18.15	2.70
2	13.52	18.08	2.85
3	16.40	18.13	2.75
4	-	18.13	2.80
5	18.07	18.40	2.80

TABLE XIV

ANALYSIS OF EXPIRED AIR PRE- AND POST-TRAINING

PATIENT 5 - D.R.

Mins. of exercise	$\dot{V}_{E_{STPD}}$ L/min.	% O_2	% CO_2
Pre-training			
Rest	5.65	17.25	3.40
1	7.08	17.25	3.25
2	9.98	17.03	3.55
3	10.04	16.88	3.90
4	11.77	17.05	3.75
5	12.32	17.05	4.00
Post-training			
Rest	6.11	16.95	3.60
1	9.33	17.58	3.05
2	11.13	17.20	3.45
3	13.39	17.05	3.80
4	13.60	17.25	3.80
5	14.52	17.20	3.90

TABLE XV

ANALYSIS OF EXPIRED AIR PRE- AND POST-TRAINING

PATIENT 6 R.M.

Mins. of exercise	$\dot{V}_{E_{STPD}}$ L/min.	% O_2	% CO_2
Pre-training			
Rest	12.48	18.45	2.50
1	10.96	18.13	2.60
2	15.27	17.55	3.10
3	17.45	17.35	3.55
4	18.64	17.60	3.50
5	19.28	17.45	3.80
Post-training			
Rest	9.90	17.85	2.75
1	11.21	17.75	2.65
2	13.88	17.30	3.25
3	15.15	17.20	3.60
4	15.59	17.20	3.80
5	16.38	17.20	4.00

TABLE XVI

BLOOD LACTATE AND PYRUVATE PRE- AND POST-TRAINING

PATIENT 1. W.B.

Time	Blood Lactate mg.%		Blood Pyruvate mg.%	
	Pre	Post	Pre	Post
Rest	9.60	12.78	1.45	1.83
Ex 1	14.52	13.68	1.36	1.70
3	18.81	21.36	1.34	1.61
5	22.36	26.74	1.51	1.70
Rec. 1	22.94	28.15	1.49	1.85
3	20.14	27.93	1.85	2.05
5	19.10	25.74	1.86	2.20
10	15.93	23.57	1.76	2.31

TABLE XVII

BLOOD LACTATE AND PYRUVATE PRE- AND POST-TRAINING

PATIENT 2 - D.E.

Time		Blood Lactate mg.%		Blood Pyruvate mg.%	
		Pre	Post	Pre	Post
Rest		4.86	7.00	0.78	1.08
Ex	1	10.49	10.05	1.07	1.16
	3	18.77	17.53	1.08	1.14
	5	24.62	21.18	1.24	1.17
Rec	1	24.98	21.70	1.45	1.36
	3	25.54	21.00	1.87	1.66
	5	24.81	19.95	2.08	1.72
	10	21.09	16.38	2.08	1.73

TABLE XVIII

BLOOD LACTATE AND PYRUVATE PRE- AND POST-TRAINING

PATIENT 3 - A.M.

Time		Blood Lactate mg.%		Blood Pyruvate mg.%	
		Pre	Post	Pre	Post
Rest		15.69	6.64	2.50	1.00
Ex	1	13.50	9.09	2.02	1.25
	3	18.88	16.27	2.02	1.26
	5	21.52	20.98	2.10	1.54
Rec	1	21.29	20.52	2.21	1.52
	3	18.86	17.24	2.41	1.75
	5	17.28	15.15	2.40	1.74
	10	14.67	11.88	2.17	1.46

TABLE XIX

BLOOD LACTATE AND PYRUVATE PRE- AND POST-TRAINING

PATIENT 4 - J.S.

Time		Blood Lactate mg.%		Blood Pyruvate mg.%	
		Pre	Post	Pre	Post
Rest		10.31	11.93	1.53	1.69
Ex	1	8.82	10.46	1.10	1.32
	3	15.31	17.07	1.23	1.37
	5	19.11	20.57	1.32	1.45
Rec	1	18.95	20.70	1.43	1.59
	3	17.58	18.40	1.72	1.91
	5	16.40	16.89	1.83	2.04
	10	13.53	13.92	1.67	1.85

TABLE XX

BLOOD LACTATE AND PYRUVATE PRE- AND POST-TRAINING

PATIENT 5 - D.R.

Time		Blood Lactate mg.%		Blood Pyruvate mg.%	
		Pre	Post	Pre	Post
Rest		5.86	4.68	0.94	0.84
Ex	1	6.06	6.03	0.84	1.04
	3	10.59	12.86	0.90	1.11
	5	13.13	16.27	1.03	1.19
Rec	1	12.37	17.51	1.04	1.25
	3	10.12	15.40	1.25	1.61
	5	9.27	12.22	1.13	1.61
	10	7.45	9.91	1.11	1.41

TABLE XXI

BLOOD LACTATE AND PYRUVATE PRE- AND POST-TRAINING

PATIENT 6 - R.M.

Time		Blood Lactate mg.%		Blood Pyruvate mg.%	
		Pre	Post	Pre	Post
Rest		13.19	7.37	1.94	0.90
Ex	1	15.21	9.83	2.01	0.87
	3	25.31	19.04	2.01	0.94
	5	35.98	27.79	2.06	1.06
Rec	1	36.68	29.63	2.10	1.12
	3	37.15	28.88	2.61	1.52
	5	35.91	27.14	3.01	1.83
	10	33.55	23.50	3.00	1.77

TABLE XXII

BODY WATER CONTENT PRE- AND POST-TRAINING

Patient	Age	Weight Kg.		Body Water L.	
		Pre	Post	Pre	Post
1. W.B.	57	63.7	63.0	35.4	35.1
2. D.E.	52	66.0	66.7	36.8	37.2
3. A.M.	61	63.6	67.3	35.0	36.4
4. J.S.	69	59.1	58.7	32.5	32.3
5. D.R.	62	60.5	61.0	33.7	33.8
6. R.M.	66	59.4	58.4	32.8	32.4

TABLE XXIII

CALCULATION OF 95% CONFIDENCE LIMITS OF CO_2 CONTENT OF EXPIRED AIR

No.	x Day 1	y Day 2
1.	4.75	4.80
2.	4.75	4.80
3.	4.75	4.80
4.	4.75	4.75
5.	4.80	4.80
6.	4.75	4.85
7.	4.75	4.75
8.	4.75	4.85
9.	4.80	4.80
10.	4.75	4.80
σ^2	.0004	.0010

$$F = \frac{\sigma y^2}{\sigma x^2} = 2.500$$

Not significant

FOR TOTAL POPULATION (Z)

1. $\sigma = 0.0317$

2. $S.E._{\bar{z}} = \sqrt{\frac{\sigma}{n}} = 0.00709$

3. 95% Confidence Limits

$= \pm t \; S.E._{\bar{z}}$

$= 2.093 \times 0.00709$

$= \pm 0.015\ \%$

4. $= \pm 0.00015$ as fraction of expired gas

TABLE XXIV

CALCULATION OF 95% CONFIDENCE LIMITS OF O_2 CONTENT OF EXPIRED AIR

No.	x Day 1	y Day 2
1.	20.00	20.05
2.	20.00	20.00
3.	19.90	19.95
4.	19.98	20.00
5.	19.90	19.95
6.	19.90	19.93
7.	19.93	19.98
8.	19.93	19.93
9.	19.93	19.95
10.	19.95	19.95
σ^2	44.27	44.31

$$F = \frac{\sigma\, y^2}{\sigma\, x^2} = 1.000$$

Not Significant

FOR TOTAL POPULATION (Z)

1. $\sigma = 0.03915$

2. $S.E._{\bar{z}} \sqrt{\frac{\sigma}{n}} = 0.00876$

3. 95% Confidence Limits

$= \pm t\ S.E._{\bar{z}}$

$= 2.093 \times 0.00876$

$= \pm .020\%$

4. $= \pm 0.00020$ as fraction of expired gas.

TABLE XXV

CALCULATION OF 95% CONFIDENCE LIMITS OF VOLUME OF EXPIRED GAS

No.	x Day 1	y Day 2
1.	13.05	13.50
2.	13.35	13.40
3.	13.35	13.35
4.	13.05	13.45
5.	13.40	13.30
6.	13.25	13.15
7.	13.10	13.50
8.	13.40	13.45
9.	13.15	13.30
10.	13.30	13.50
σ^2	19.50	19.94
$F = \frac{\sigma y^2}{\sigma x^2} = 1.023$		
Not significant		

FOR TOTAL POPULATION (Z)

1. $\sigma = 0.1433$

2. $S.E._{\bar{z}} = \sqrt{\frac{\sigma}{n}} = 0.032$

3. 95% Confidence Limits

$= \pm t \; S.E._{\bar{z}}$

$= 2.093 \times 0.032$

4. $= \pm$ 0.07 Litres

TABLE XXVI

CALCULATION OF 95% CONFIDENCE LIMITS OF BLOOD LACTATE DETERMINATION

No.	Analysis 1	Analysis 2
1.	11.94	11.92
2.	10.66	10.26
3.	17.22	16.92
4.	20.63	20.51
5.	18.62	18.19
6.	17.12	16.67
7.	13.94	13.89
8.	5.06	4.66
9.	10.50	10.48
10.	18.81	18.72

1. $\sigma = \sqrt{\frac{\text{E (Differences Between Duplicates)}2}{2 \times \text{No. of Pairs}}}$

$= 0.2028$

2. 95% Confidence Limits

$= \pm 3\sigma$

$= \pm 3 \times 0.2028$

$= \pm 0.60$ mg.

$= \pm 0.060$ mEq.

TABLE XXVII

CALCULATION OF 95% CONFIDENCE LIMITS OF BLOOD PYRUVATE DETERMINATION

No.	Analysis 1	Analysis 2
1.	1.69	1.68
2.	1.32	1.31
3.	1.37	1.36
4.	1.46	1.44
5.	1.60	1.58
6.	1.92	1.90
7.	2.05	2.03
8.	1.86	1.84
9.	0.78	0.77
10.	1.07	1.07

1. $\sigma = \sqrt{\frac{\text{E(Differences Between Duplicates) 2}}{\text{2 x No. of pairs}}}$

$= 0.01095$

2. 95% Confidence Limits

$= \pm 3\sigma$

$= \pm 3 \times 0.01095$

$= \pm 0.03$ mg.

$= \pm 0.003$ mEq.

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